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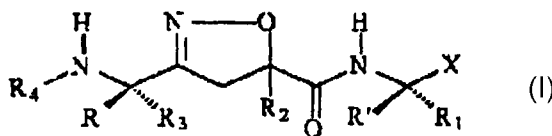
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(54) Title: CASPASE INHIBITOR



(57) Abstract: The present invention relates to an isoxazoline derivative of formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof, and the use of the derivative in inhibiting the activity of caspases. The derivative according to the present invention can be effectively used in treating diseases due to caspases, such as, for example the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injury by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

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## CASPASE INHIBITOR

### Technical Field

The present invention relates to a novel isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof which can serve as an inhibitor for protein caspases (cysteinyI-aspartate proteinases) and a process for preparing the same and the use of the derivative as an inhibitor for caspases. The derivative according to the present invention can be effectively used in treating diseases due to caspases, such as, for example the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

### Background Art

All organisms in nature undergo the life cycle consisting of development, differentiation, growth and death. Recently, an extensive research has been made to a mechanism involved in apoptosis which would play a key role in the control of the life cycle and the outbreak of diseases. It has been reported that apoptosis is occurred by a number of factors, but largely due to the three kinds of cellular signal transport systems: the first of which is a signal transport system by the protein-protein interaction (See, Muzio M. et al., *Cell* 85, 817, 1996; Humke E.W. et al., *JBC* 273, 15702, 1998), the second, an incorporation of cytochrome C into cytoplasm via mitochondria (See, Liu X. et al., *Cell* 86:147, 1996; Li P. et al., *Cell* 91, 479, 1997), and the third, a cellular signal transport pathway by the SAPK(Stress-activated protein kinases) activation of mitogen-activation

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protein kinase(MAPK) enzymes. All the pathways have been known to activate caspases cascade. As such caspases, about 10 kinds of isoenzymes have been identified in human and 14 kinds in mouse (see, Thornberry N.A. et al., *Science* 28, 1312 1998; Green D.R. *Science* 28, 1309, 1998; Ahmad M., et al., *Cancer Res.* 15, 5201 1998). The enzymes exist in the form of proenzyme which has no enzymatic activity within the cells and converted to an activated form if the cells are damaged or are exposed to a substance which leads to cellular necrosis. An activated enzyme has a heterodimer structure in which two polypeptides, i.e. larger subunits with the molecular weight of about 17-20 kDa, and smaller subunits with the molecular weight of about 10 kDa are bound together.

As present, caspases are classified into three (3) groups in view of the genetic identification analysis results and the biochemical characteristics: the first group is caspase-1, 4 and 5 which are responsible for the processing of cytokine activation, the second is caspase-3, 6 and 7 which carry out apoptosis and the third is caspase-8, 9 and 10 which are responsible for enzymatic activation in the upstream of signal transport system of apoptosis.

Among these caspases, Caspase-3 group and Caspase-8, 9, 10 etc. were recently reported to be related to apoptosis, and diseases (see, Thornberry N.A. et al., *Science*, 28, 1312, 1998).

According the recent research results, caspases are commonly activated as apoptosis is initiated, even if there is a minor difference depending upon the tissues and cells. The activated caspases then activate intracellular CAD(Caspase-activated DNase) which finally digests intranuclear DNA to

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result in cell death (Sakahira H., et al., *Nature* 1 96, 1998; Enari M et al., *Nature* 1 43, 1998). In addition, they promotes apoptosis by decomposing substrates such as PARP (Poly-ADP ribose polymerase) which is necessary for the survival of cells.

Meantime, according to the recent disease-related researches, it was reported that the activity of Caspase-3 is increased in the brain of dementia patient which promotes the production of beta amyloid peptide from beta amyloid precursor protein that is considered to be a major cause of dementia, thereby accelerating the apoptosis of brain cells (see, Kuida K. et al., *Nature* 28, 368, 1996). Further, it was reported that activation of caspases can be the direct inducer of various diseases such as sepsis (see, Haendeler J. et al., *Shock* 6, 405, 1996; Lenhoff R.J. et al., 29, 563, 1999), rheumatoid arthritis (Firestein G.S. et al., *J. Clin. Invest* 96(3), 1631, 1995), cerebral stroke (see, Hill I.E. et al., *Brain Res.* 10, 398, 1995), ALS disease (see, Alexianu M.E. et al., *J. Neurochem* 63, 2365, 1994), autoimmune disease (see, Rieux-Laucat F, et al., *Science* 2, 1347, (1995), diabetes mellitus (see, Juntti-Berggren et al., *Science* 2, 86, 1993), hepatitis (Haendeler J. et al., *Shock* 6, 405, 1996), organ transplantation rejection reaction (Koglin J. et al., *Transplantation*, 27, 904, 1999; Bergese S.D. et al., *Transplantation* 27, 904, 1999), gastric ulcer (see, Slomiany B.L. et al., *J. Physiol. Pharmacol.* 96, 1631, 1995), and the like.

The researches on three dimensional structure of caspase-1 and caspase-3, catalytic mechanism of the enzyme and enzyme-substrate specificity (see, Wilson, K.P et al., *Nature* 370, 270, 1994; Walker, N.P.C. et al., *Cell* 78, 343, 1994; *Nature Struc. Biol.* 3, 619, 1996) revealed that Caspase-1 group has hydrolase-substrate specificity for the peptide sequence of (P4)-Val-X-Asp(P1) and Caspase-3 group has hydrolase-substrate specificity

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for the sequence of (P4)Asp-X-X-Asp(P1).

Z-VAD-fluoromethylketone, Z-DEVD-fluoromethyl ketone which mimics the above amino acid sequence have already been used in the researches on the inhibitors and were proven to have an inhibitory activity on apoptosis of hepatic cells by an activation of caspases (see, Rodriguez I. Et al., *J. Exp. Med.*, 184, 2067, 1996; Rouquet N. et al., *Curr Biol.* 1, 1192, 1996; Kunstle G. et al., *Immunol. Lett* 55, 5, 1997), and on the apoptosis of brain cells by cerebral ischemias.

However, since such peptide derivatives are deficient in drug property for clinical application, they cannot be used as therapeutics.

### **Disclosure of Invention**

It is therefore an object of the present invention to provide a novel heterocyclic compound of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof which are useful as a caspase inhibitor.

Another object of the present invention is to provide a process for preparing the compound of formula (I).

Still another object of the present invention is to provide a pharmaceutical composition for inhibiting caspases activity which comprises as the active ingredient a therapeutically effective amount of a derivative of formula (I) and pharmaceutically acceptable carrier.

Further objects and advantages of the invention will become apparent

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through reading the remainder of the specification.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the more pertinent features of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or by modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be found by referring to the detailed description of the preferred embodiment in addition to the scope of the invention defined by the claims.

### **BEST MODE FOR CARRYING OUT THE INVENTION**

Hereinafter, the invention will be illustrated in more detail.

The present inventors have conducted an extensive research for many years in order to develop new therapeutics suitable for caspase inhibitor which has a unique structure over those known in the art. As a result, the inventors have surprisingly discovered a novel isoxazoline derivative of formula (I) which has a different structure over the known inhibitors and has excellent inhibitory activity against various substrates for caspases, and have completed the present invention.

In advance of illustrating the present invention, some important terms are defined as follows:

a) Simple Alkyl Chain (hereinafter referred to as "SAC") is meant by a carbohydrate having C<sub>1-8</sub>, and contains a branched isomeric form.

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b) Simple CycloAlkyl Chain (hereinafter referred to as "SCAC" is meant by a cyclic compound having C<sub>3-10</sub>.

c) Aryl group (hereinafter referred to as "Ar") represents benzene [1:2,3,4,5,6], naphthalene[1,2:1,2,3,4,5,6,7,8,], pyridine [2,3,4:2,3,4,5,6], indole[1,2,3,4,5,6,7: 1,2,3,4,5,6,7], quinoline[2,3,4,5,6,7,8: 2,3,4,5,6,7,8], isoquinoline[1,3,4,5,6,7,8: 1,3,4,5,6,7,8], furan [2,3:2,3,4,5], thiophene[2,3:2,3,4,5], pyrrole[1,2,3: 1,2,3,4,5], pyrimidine [2,4,5,6: 2,4,5,6], imidazole[1,2,4,5:1,2,4,5], etc. in which the former digits within the bracket represents a position where the corresponding aryl group is connected to the inhibitor according to the present invention and the latter digits after the colon represents a position where the substituent Y defined later can be attached.

Frequently referred terms are abbreviated as follows:

N-chlorosuccinimide : NCS

N-methylmorpholine : NMM

N,N-dimethyl formamide : DMF

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide: EDC

1-hydroxybenzotriazole hydrate : HOBt

Trifluoroacetic acid : TFA

t-butoxycarbonyl : Boc

benzyloxycarbonyl : Cbz

methyl : Me

ethyl : Et

equivalent : Eq or eq

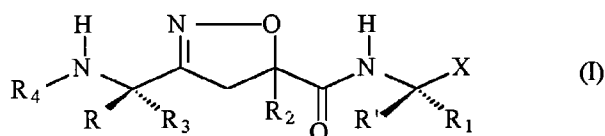
The term "stereochemically isomeric forms" as used in the foregoing and

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hereinafter defines all the possible isomeric forms which the derivative of formula (1) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixture containing all diastereomers of the basic molecular structure. Stereochemically isomeric forms of the derivatives of the formula (1) are intended to be embraced within the scope of this invention.

The pharmaceutically acceptable salts as used in the foregoing and hereinafter comprises the therapeutically active non-toxic salt forms which the derivative of formula (1) are able to form.

In an aspect, the present invention provides a novel isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof.



In the compound of formula (I), the substituents are defined as follows.

R and R' each independently represents simple alkyl chain (-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar) or hydrogen, preferably represents hydrogen. Throughout the description of the specification, R' has the same meaning as R unless specifically defined.

R<sub>1</sub> represents -SAC, -SCAC, -Ar, or -SAC-Ar and/or contains side chain residues of natural amino acids, preferably represent -CH<sub>2</sub>COOH.

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R<sub>3</sub> represents -SAC, -SCAC, -Ar, or -SAC-Ar and/or contains side chain residues of natural amino acids, preferably represent -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>COOH, -(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>C(=O)NH<sub>2</sub> or -(CH<sub>2</sub>)<sub>2</sub>C(=O)NH<sub>2</sub>.

In a case where an adjacent position of R<sub>1</sub> or R<sub>3</sub> become a stereogenic center, both the stereoisomeric compounds are intended to be embraced within the scope of the present invention. Similarly, a case where two forms of compounds are co-exist (a mixture of diastereomeric compounds) is embraced within the scope of the invention. In addition, the cases where R<sub>1</sub> or R<sub>3</sub> are composed of carboxylic acids or bases with side chain residue of amino acids, their protected forms such as simple esters or pharmaceutically acceptable salt forms are also embraced within the scope of the compounds according to the invention.

R<sub>2</sub> represents -H, -SAC, -SCAC, -Ar, or -SAC-Ar and contains side chain residues of natural amino acids. In a case where an adjacent position due to R<sub>2</sub> become a stereogenic center, both the stereoisomeric compounds are embraced within the context of the compounds of the present invention, Similarly, a case where two forms of compounds are co-exist (a mixture of diastereomeric compounds) is embraced within the category of the compounds according to the invention. In addition, the cases where R<sub>2</sub> are composed of carboxylic acids or bases with side chain residue of amino acid, their protected forms such as simple esters or pharmaceutically acceptable salt forms are also embraced within the scope of the compounds according to the invention.

R<sub>2</sub> further represents -(CH<sub>2</sub>)<sub>n</sub>(O)<sub>m</sub>R<sub>5</sub> (in which R<sub>5</sub> = -SAC, -SCAC, -Ar, -SAC-Ar; and n=0, 1, 2; m=0, 1), or -(CH<sub>2</sub>)<sub>n</sub>OC(=O)R<sub>6</sub> (in which R<sub>6</sub> =

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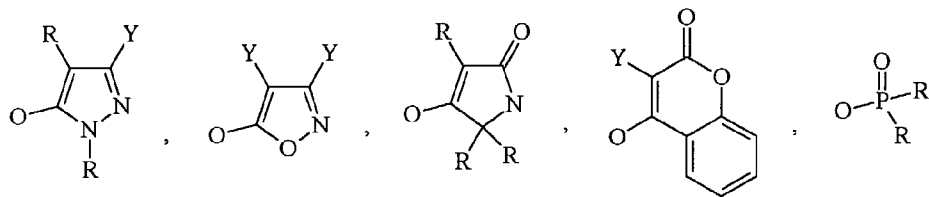
-SAC, -SCAC, -Ar, or -SAC-Ar; and  $n=1, 2$ ). Preferable  $R_2$  represents  $(CH_2)_n(O)_mAr'$  (in which  $n=0, 1, 2$ ;  $m = 0, 1$ ;  $Ar' =$  substituted phenyl or imidazole), methyl or hydrogen.

$R_4$  represents an organic acid acyl group of all the natural amino acids or represents  $-C(=O)R_7$  (in which  $R_7 = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ),  $-C(=O)OR_8$  (in which  $R_8 = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ),  $-C(=O)NR_9R_{10}$  (in which  $R_9, R_{10} = -H, -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ),  $-SOR_{11}$  (in which  $R_{11} = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ), or  $-SO_2R_{12}$  (in which  $R_{12} = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ).

In cases where  $R_1$  and the adjacent  $R'$ , and/or  $R_3$  and the adjacent  $R$  are connected to each other to form a cyclic compound,  $R_1-R'$  or  $R_3-R$  together represents  $(CH_2)_n$ ,  $(CH_2)_n-O-(CH_2)_m$ , or  $(CH_2)_n-NR_{13}-(CH_2)_m$  [in which  $n+m < 9$ ,  $R_{13} = -SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, \text{ or } -C(=O)-SAC-Ar$ ].

$X$  represents  $-CN, -CHO, -C(=O)R_{14}$  [in which  $R_{14} = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ],  $-C(=O)OR_{15}$  [in which  $R_{15} = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ],  $-CONR_{16}R_{17}$  [in which  $R_{16}$  and  $R_{17}$  each represents  $-H, -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ],  $-C(=O)CH_2OR_{18}$  [in which  $R_{18}$  represents  $-SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ], or  $-C(=O)CH_2OC(=O)R_{19}$  [in which  $R_{19} = -SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$ ]. The invention further encompasses a case where if  $X$  represents  $-COCH_2-W$ ,  $W$  represents  $-N_2, -F, -Cl, -Br, -I, -NR_{20}R_{21}$  or  $-SR_{22}$  [in which wherein  $R_{20}, R_{21}$  and  $R_{22}$  each independently represents  $-SAC, -SCAC, -Ar, \text{ or } -SAC-Ar$  or a case where  $R_{20}$  and  $R_{21}$  are connected to form a cyclic compounds].  $W$  also represents

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in which Y represents -OH,  $\text{OR}_{23}$  (in which  $\text{R}_{23} = \text{-SAC}$ , or  $\text{-SCAC}$ ),  $\text{-C(=O)R}_{24}$  (in which  $\text{R}_{24} = \text{-H}$ ,  $\text{-SAC}$ , or  $\text{-SCAC}$ ),  $\text{-F}$ ,  $\text{-Cl}$ ,  $\text{-Br}$ ,  $\text{-I}$ ,  $\text{-CN}$ ,  $\text{-NC}$ ,  $\text{-N}_3$ ,  $\text{-CO}_2\text{H}$ ,  $\text{CF}_3$ ,  $\text{-CO}_2\text{R}_{25}$  (in which  $\text{R}_{25} = \text{-SAC}$ , or  $\text{-SCAC}$ ),  $\text{-C(=O)NHR}_{26}$  (in which  $\text{R}_{26} = \text{-SAC}$ , or  $\text{-SCAC}$ ), and  $\text{-C(=O)NR}_{27}\text{R}_{28}$  (in which  $\text{R}_{27}$ ,  $\text{R}_{28} = \text{-SAC}$ , or  $\text{-SCAC}$ ) and can be mono- or poly-substituted at its maximum regardless of the order and the kinds.

Among the compound of formula (I), preferred are those in which

- R and R' represent hydrogen,
- $\text{R}_1$  represents  $\text{-CH}_2\text{COOH}$ ,
- $\text{R}_2$  represents  $(\text{CH}_2)_n(\text{O})_m\text{Ar}'$  [in which  $n=1, 2$ ;  $m=0, 1$ ;  $\text{Ar}' =$  substituted phenyl or imidazole], methyl or hydrogen,
- $\text{R}_3$  represents  $\text{-CH}(\text{CH}_3)_2$ ,  $\text{-CH}_2\text{COOH}$ ,  $\text{-(CH}_2)_2\text{CO}_2\text{H}$ ,  $\text{-CH}_2\text{C(O)NH}_2$  or  $\text{-(CH}_2)_2\text{C(O)NH}_2$ ,
- $\text{R}_4$  represents  $\text{-C(=O)(O)}_n\text{R}_{29}$  [in which  $n=0, 1$ ;  $\text{R}_{29} = \text{-Ar}$ , or  $\text{-SAC-Ar}$ ],  $\text{-SO}_2\text{R}_{30}$  [in which  $\text{R}_{30} = \text{-Ar}$ , or  $\text{-SAC-Ar}$ ], or  $\text{-C(=O)NHR}_{31}$ , [in which  $\text{R}_{31} = \text{-Ar}$ , or  $\text{-SAC-Ar}$ ],
- X represents  $\text{-C(=O)CHN}_2$ ,  $\text{-C(=O)CH}_2\text{Br}$ ,  $\text{-C(=O)CH}_2\text{Cl}$ ,  $\text{-C(=O)CH}_2\text{OAr}''$  [ $\text{Ar}'' =$  preferably phenyl] or  $\text{-C(=O)CH}_2\text{OC(=O)Ar}'''$  [in which  $\text{Ar}''' =$  preferably 2,6-dichlorophenyl or 2,6-dimethylphenyl].

Most preferred compounds are selected from the group consisting of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid;

(2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 1-(N-methyl-N-methoxy)-amide;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic

acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-sulfonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(2S)-2-acetylamino-succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-

isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (diastomeric mixture);  
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid

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(diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-bromo-pentanoic acid

(diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarboxylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarboxylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarboxylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarboxylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarboxylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarboxylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-

pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-

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imidazolyl-methyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;  
(3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;  
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid; and  
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidiny)-pentanoic acid.

In another aspect, the present invention provides a process for preparing a compound of formula (I).

Hereinbelow, a process for preparing the isoxazoline derivatives of formula (I) according to the present invention will be explained with respect to Reaction Schemes 1 and 2. It should be understood that the reaction schemes generally illustrate the specific process used in the present invention, but any modification of the unit operations may be made without departure of the spirit of the invention. Therefore, the present invention should not be limited to the following preferred embodiments.

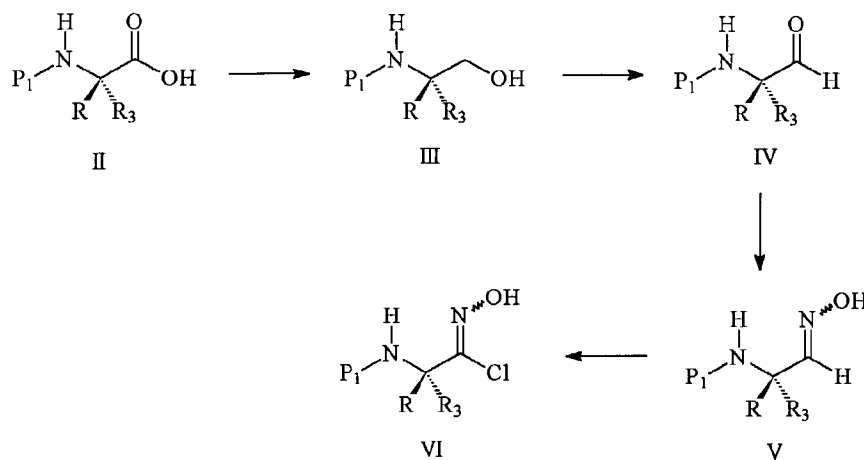
In the first step, amino protected amino acid (II) (commercially available from Novabiochem) is reduced to give N-protected amino alcohol (III) which is then oxidized to give N-protected amino aldehyde (IV).

N-protected amino aldehyde (IV) is reacted with hydroxylamine-hydrochloride and sodium carbonate in a mixed solution of an alcohol and

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water to give an oxime (V) (syn- and anti-oxime). The resulting oxime derivative (V) is treated with NCS (N-chlorosuccinimide) in an aqueous solution of dimethylformamide to give hydroxamoyl chloride (VI). As the representative substituents used in the synthesis of hydroxamoyl chloride, the following groups may be exemplified:  $P_1$  represents Cbz, t-Boc, Fmoc, Teoc(trimethylsilyl-ethyloxycarbonyl), etc.; R represents H and  $R_3$  represents  $-\text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $-\text{CH}_2\text{CO}_2\text{Me}$ ,  $-\text{CH}_2\text{CO}_2\text{Bu(t)}$ , -isopropyl, phenylmethyl, and the like.

## Reaction Scheme 1



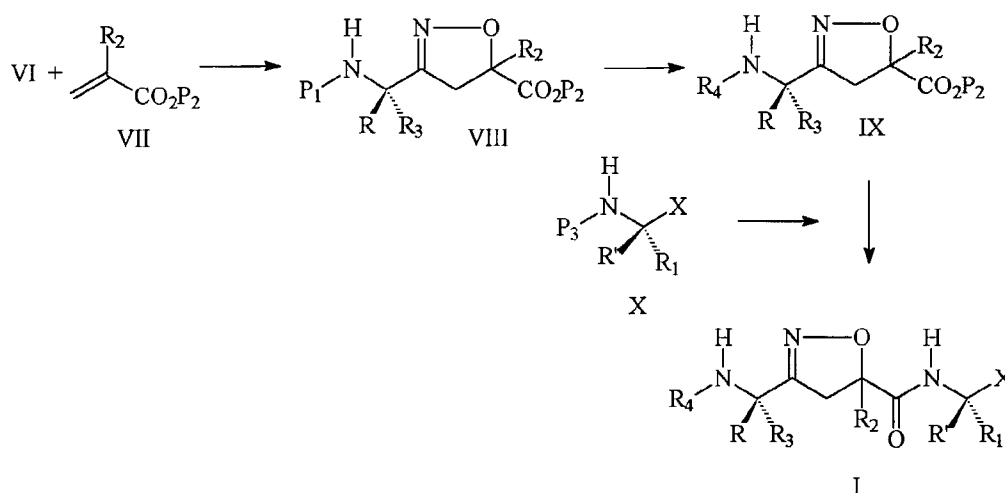
In the above Reaction Scheme 1, the following combinations of a) to g) for the commercially available compounds (II) to (VI) may be synthesized.

- a)  $P_1 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = i\text{-Pr}$
- b)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = i\text{-Pr}$
- c)  $P_1 = \text{Fmoc}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$
- d)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CO}_2\text{Me}$

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- e)  $P_1 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CO}_2\text{Bu(t)}$   
 f)  $P_1 = \text{Fmoc}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CO}_2\text{Bu(t)}$   
 g)  $P_1 = \text{Boc}$  or  $\text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{Ph}$

## Reaction Scheme 2



In the second step, the hydroxamoyl chloride (VI) thus obtained is then reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII). If necessary, isoxazoline derivative (VIII) may be synthesized directly from the oxime derivative (V).

If a compound having the protecting group  $P_1$  can be used as the inhibitor (for example,  $P_1$  is a Cbz group), the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and if it is necessary to convert the protecting group  $P_1$  into other substituent,  $P_1$  is removed and  $R_4$  is introduced thereinto.

In the above Reaction Scheme 2, the following combination of substituents

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may be synthesized.

In the compound (VIII),

- a)  $P_1 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{H}$ ,  $P_2 = \text{Et}$
- b)  $P_1 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{H}$ ,  $P_2 = \text{H}$
- c)  $P_1 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{Et}$
- d)  $P_1 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{H}$
- e)  $P_1 = \text{Fmoc}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  $P_2 = \text{CH}_3(\text{or Et})$
- f)  $P_1 = \text{Teoc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_3$ ,  $P_2 = \text{H}$
- g)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- h)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $P_2 = \text{Et}$
- i)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{1-naphthyl}$ ,  $P_2 = \text{Et}$
- j)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{2-naphthyl}$ ,  $P_2 = \text{Et}$
- k)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{phenyl}$ ,  $P_2 = \text{Et}$
- l)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{4-bromophenyl}$ ,  $P_2 = \text{Et}$
- m)  $P_1 = \text{t-Boc}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{AcOCH}_2$ ,  $P_2 = \text{Et}$

In the compound (IX),

- a)  $R_4 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{H}$ ,  $P_2 = \text{Et}$
- b)  $R_4 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{H}$ ,  $P_2 = \text{H}$
- c)  $R_4 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{Et}$
- d)  $R_4 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{H}$
- e)  $R_4 = \text{1-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{Et}$
- f)  $R_4 = \text{1-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{H}$
- g)  $R_4 = \text{2-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{Et}$
- h)  $R_4 = \text{2-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = \text{i-Pr}$ ,  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{H}$
- i)  $R_4 = \text{2-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  $P_2 = \text{CH}_3$
- j)  $R_4 = \text{2-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  $P_2 = \text{H}$

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- k)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- l)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- m)  $R_4 = 2\text{-naphthalenesulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $P_2 = \text{Et}$
- n)  $R_4 = 2\text{-naphthalenesulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $P_2 = H$
- o)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $P_2 = \text{Et}$
- p)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $P_2 = H$
- q)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $P_2 = \text{Et}$
- r)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $P_2 = H$
- s)  $R_4 = \text{hydrocinnamoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- t)  $R_4 = \text{hydrocinnamoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- u)  $R_4 = 1\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- v)  $R_4 = 1\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- w)  $R_4 = 1\text{-naphthalenesulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- x)  $R_4 = 1\text{-naphthalenesulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- y)  $R_4 = 3\text{-indoleacetyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- z)  $R_4 = 3\text{-indoleacetyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- aa)  $R_4 = 3\text{-indolepropionyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- ab)  $R_4 = 3\text{-indolepropionyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- ac)  $R_4 = \text{trans-cinnamoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- ad)  $R_4 = \text{trans-cinnamoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- ae)  $R_4 = \text{phenylmethylsulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- af)  $R_4 = \text{phenylmethylsulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- ag)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $P_2 = \text{Et}$
- ah)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $P_2 = H$
- ai)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = \text{Et}$
- aj)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $P_2 = H$
- ak)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = 1\text{-imidazolyl}$ ,  $P_2 = \text{Et}$
- al)  $R_4 = 1\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = 1\text{-imidazolyl}$ ,  $P_2 =$

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H

am)  $R_4 = \text{COCH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  
 $P_2 = \text{CH}_3$

an)  $R_4 = \text{COCH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R = \text{H}$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  
 $P_2 = \text{H}$

ao)  $R_4 = \text{COCH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R = \text{H}$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{CH}_3$ ,  $P_2 = \text{CH}_3$

ap)  $R_4 = \text{COCH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R = \text{H}$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{CH}_3$ ,  $P_2 = \text{H}$

In the compound (X),

a)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CO}_2\text{Me}$

b)  $P_3 = \text{HCl+H}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CO}_2\text{Me}$

c)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{COCH}_2\text{N}_2$

d)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{COCH}_2\text{Br}$

e)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{COCH}_2\text{OPh}$

f)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CH(OH)CH}_2\text{OPh}$

g)  $P_3 = \text{H}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CH(OH)CH}_2\text{OPh}$

h)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,

$X = \text{CH(OH)CH}_2\text{OC(O)Ph(2,6-dichloro)}$

i)  $P_3 = \text{H}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,

$X = \text{CH(OH)CH}_2\text{OC(O)Ph(2,6-dichloro)}$

j)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CONMe(OMe)}$

k)  $P_3 = \text{H}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CONMe(OMe)}$

l)  $P_3 = \text{Cbz}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CH(OH)CH}_2\text{O- (1-naphthyl)}$

m)  $P_3 = \text{H}$ ,  $R = \text{H}$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CH(OH)CH}_2\text{O- (1-naphthyl)}$

In the compound (I),

a)  $R_4 = 2\text{-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,

$X = \text{CO}_2\text{H}$

b)  $R_4 = 2\text{-naphthoyl}$ ,  $R = \text{H}$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,

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- $X = C(=O)CH_2N_2$
- c)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = C(=O)CH_2Br$
- d)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = C(=O)CH_2OPh$
- e)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = C(=O)CH_2OC(=O)Ph$  (2,6-dichloro)
- f)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = 2\text{-naphthyloxymethylcarbonyl}$
- g)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = 1\text{-naphthyloxymethylcarbonyl}$
- h)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = CH(OH)CH_2OPh$
- i)  $R_4 = 1\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = C(=O)CH_2OPh$
- j)  $R_4 = 2\text{-naphthalenesulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = CH(OH)CH_2OPh$
- k)  $R_4 = 2\text{-naphthalenesulfonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = C(=O)CH_2OPh$
- l)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = CH(OH)CH_2OPh$
- m)  $R_4 = 2\text{-quinolinecarbonyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhOCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  
 $X = CH(OH)CH_2OPh$
- n)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  $X = C(=O)CH_2N_2$
- o)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  $X = C(=O)CH_2Br$
- p)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = PhCH_2$ ,  $R_1 = CH_2CO_2Bu(t)$ ,  $X = C(=O)CH_2OPh$

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- q)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{OC(=O)-Ph-(2,6-dichloro)}$
- r)  $R_4 = \text{N-acetyl-}\beta\text{-t-butyl aspartyl}$ ,  $R = H$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CH(OH)CH}_2\text{OPh}$
- s)  $R_4 = \text{N-acetyl-}\beta\text{-t-butyl aspartyl}$ ,  $R = H$ ,  $R_3 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $R_2 = \text{CH}_3$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{OPh}$
- t)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)NMe(OMe)}$
- u)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_3$
- v)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CO}_2\text{CH}_3$
- w)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CO}_2\text{H}$
- 10x)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{N}_2$
- y)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{Br}$
- z)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{OC(=O)-Ph-2,6-dichloro}$
- aa)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)NMe(OMe)}$
- ab)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = \text{PhOCH}_2$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_3$
- ac)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{CO}_2\text{CH}_3$
- ad)  $R_4 = \text{Cbz}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{OC(=O)Ph(2,6-dichloro)}$
- ae)  $R_4 = 2\text{-naphthoyl}$ ,  $R = H$ ,  $R_3 = i\text{-Pr}$ ,  $R_2 = H$ ,  $R_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $X = \text{C(=O)CH}_2\text{OPh}$

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- af)  $R_4$  = hydrocinnamoyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  = CH<sub>2</sub>CO<sub>2</sub>Bu(t),  
 $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- ag)  $R_4$  = 1-naphthoyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  = CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$   
 $=$  C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- ah)  $R_4$  = 1-naphthalenesulphonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- ai)  $R_4$  = 3-indoleacetyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  = CH<sub>2</sub>CO<sub>2</sub>Bu(t),  
 $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- aj)  $R_4$  = 3-indolepropionyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- ak)  $R_4$  = *trans*-cinnamoyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- al)  $R_4$  = phenylmethylsulfonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- am)  $R_4$  = 2-quinolinecarbonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = H,  $R_1$  = CH<sub>2</sub>CO<sub>2</sub>Bu(t),  
 $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- an)  $R_4$  = 2-quinolinecarbonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = H,  $R_1$  = CH<sub>2</sub>CO<sub>2</sub>Bu(t),  
 $X$  = C(=O)CH<sub>2</sub>OPh
- ao)  $R_4$  = 2-quinolinecarbonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OC(=O)Ph(2,6-dichloro)
- ap)  $R_4$  = 2-quinolinecarbonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = PhCH<sub>2</sub>,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OPh
- aq)  $R_4$  = 2-quinolinecarbonyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = 1-imidazolyl,  $R_1$  =  
CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OCPH
- ar)  $R_4$  = 2-naphthoyl,  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = H,  $R_1$  = CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  =  
C(=O)CH<sub>3</sub>
- as)  $R_4$  = COCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $R$  = H,  $R_3$  = (CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $R_2$  = CH<sub>3</sub>,  $R_1$   
 $=$  CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $X$  = C(=O)CH<sub>2</sub>OPh
- at)  $R_4$  = COCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Bu(t),  $R$  = H,  $R_3$  = i-Pr,  $R_2$  = CH<sub>3</sub>,  $R_1$  =

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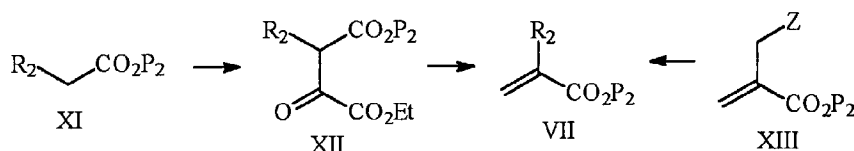
$\text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $\text{X} = \text{C}(=\text{O})\text{CH}_2\text{OPh}$

au)  $\text{R}_4 = 1\text{-naphthoyl}$ ,  $\text{R} = \text{H}$ ,  $\text{R}_3 = i\text{-Pr}$ ,  $\text{R}_2 = \text{PhCH}_2$ ,  $\text{R}_1 = \text{CH}_2\text{CO}_2\text{Bu(t)}$ ,  $\text{X} = \text{C}(=\text{O})\text{CH}_2\text{N}(\text{CH}_2)_5$

In Reaction Scheme 2, the functional group X of compound (X) may be introduced by several unit operations after the reactions involved in the synthesis of the compound (VIII) or (IX), or the compound (VIII) or (IX) already having desired substituent X may be proceed with the subsequent reactions.

The acrylate derivative (VII) may be synthesized by any of two processes as depicted in Reaction Scheme 3 below.

### Reaction Scheme 3



Ester derivative (XI) is reacted with diethyl oxalate to give oxalate derivative (XII) which is then reacted in the presence of a base to give desired acrylate derivative (VII). Alternatively, it may be synthesized by various process starting from the known compound (XIII). That is, the known compound (XIIIa) is easily converted into compounds (XIIIb), (VIIe), (VIIf), (VIIg), etc.

In the compounds (XI) and (XII), the substituents are exemplified as follows:

a)  $\text{P}_2 = \text{Et}$ ,  $\text{R}_2 = \text{Ph}$

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- b)  $P_2 = \text{Et}$ ,  $R_2 = 4\text{-bromophenyl}$
- c)  $P_2 = \text{Et}$ ,  $R_2 = 1\text{-naphthyl}$
- d)  $P_2 = \text{Et}$ ,  $R_2 = 2\text{-naphthyl}$

In the compounds (VII) and (XIII), the following combination of the substituents can be synthesized by the above process.

In the compound of (VII),

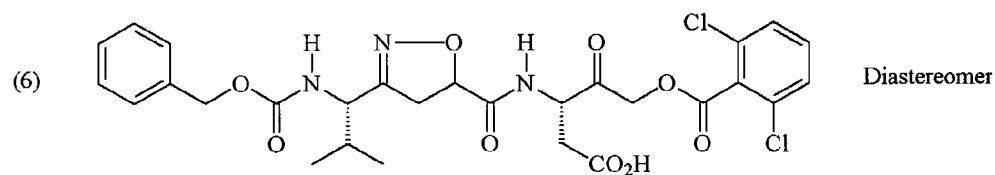
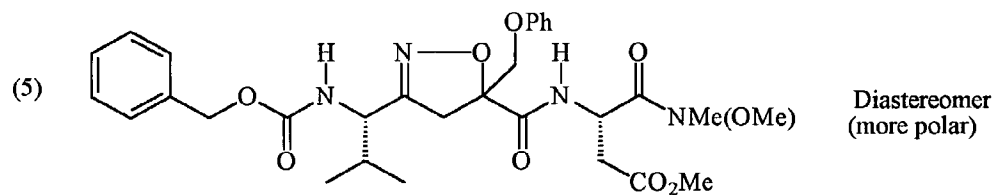
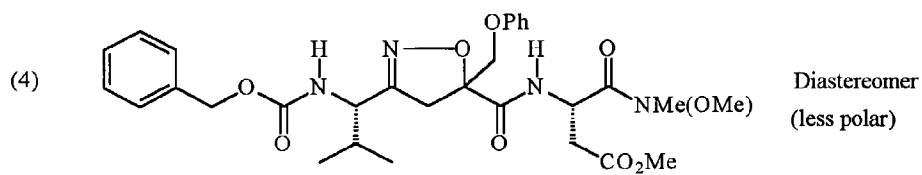
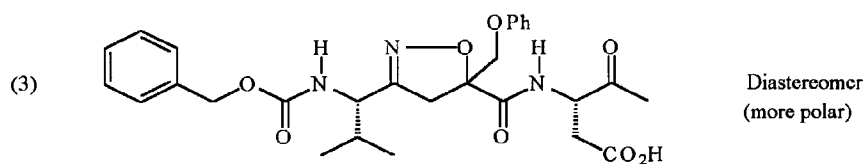
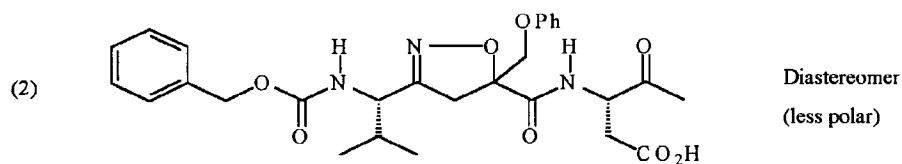
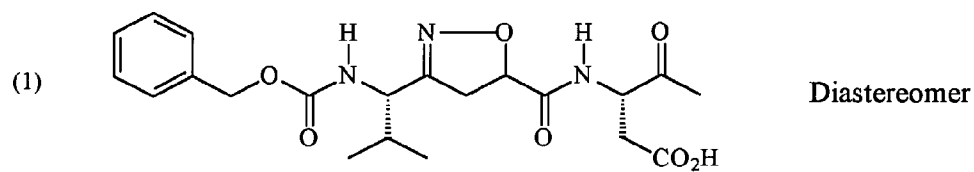
- a)  $R_2 = \text{Ph}$ ,  $P_2 = \text{Et}$
- b)  $R_2 = 4\text{-bromophenyl}$ ,  $P_2 = \text{Et}$
- c)  $R_2 = 1\text{-naphthyl}$ ,  $P_2 = \text{Et}$
- d)  $R_2 = 2\text{-naphthyl}$ ,  $P_2 = \text{Et}$
- e)  $R_2 = \text{CH}_2\text{OAc}$ ,  $P_2 = \text{Et}$
- f)  $R_2 = \text{CH}_2\text{Ph}$ ,  $P_2 = \text{Et}$
- g)  $R_2 = \text{CH}_2\text{OPh}$ ,  $P_2 = \text{Et}$

In the compound (XIII),

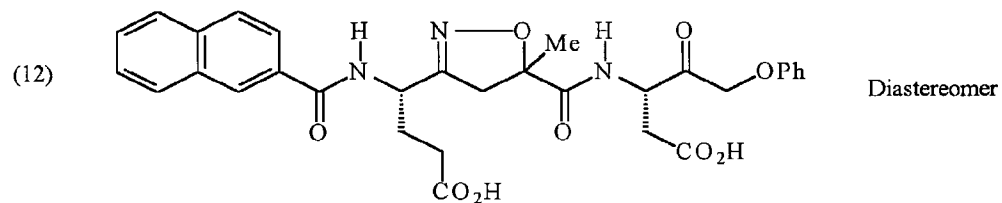
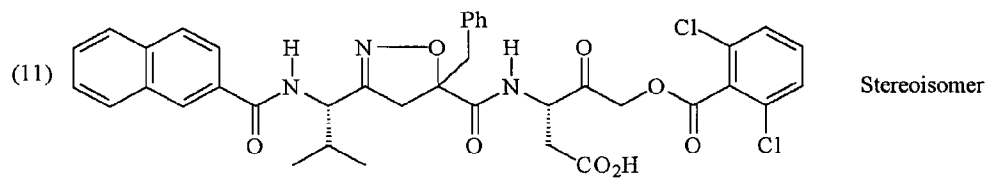
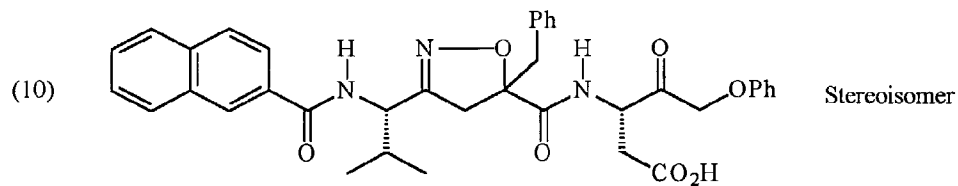
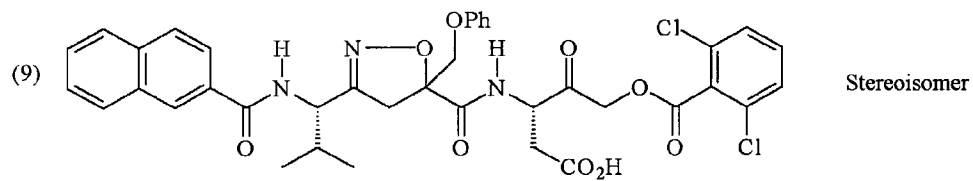
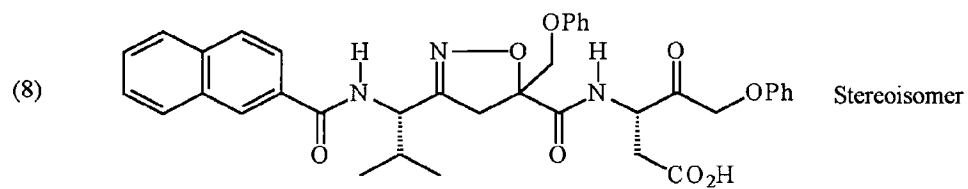
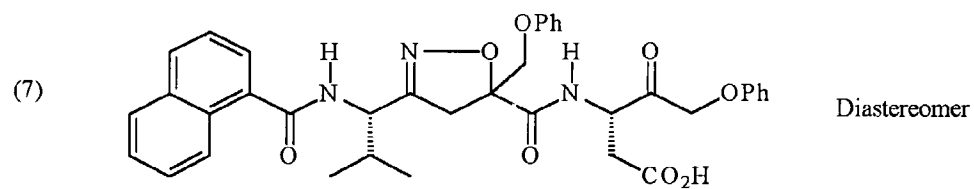
- a)  $P_2 = \text{Et}$ ,  $Z = \text{OH}$
- b)  $P_2 = \text{Et}$ ,  $Z = \text{Br}$

Hereinafter, the representative compounds synthesized by the process of the invention will be listed with respect to their structural formulae. However, they are presented for the purpose of illustration of the synthesis of the compounds of the invention and for substantiating the fact that the compounds of the invention can be synthesized by the above mentioned preparation process, but the present invention should not be limited to the compounds listed in any manner.

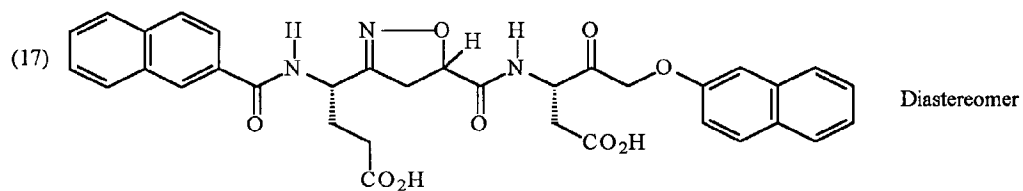
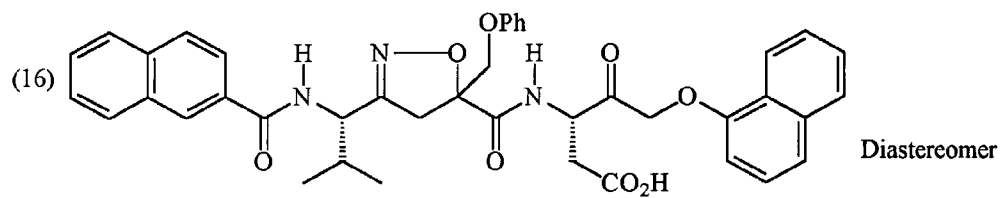
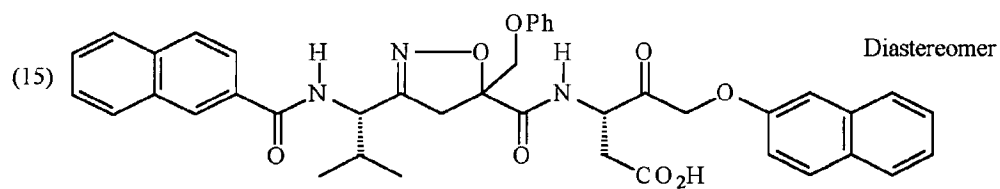
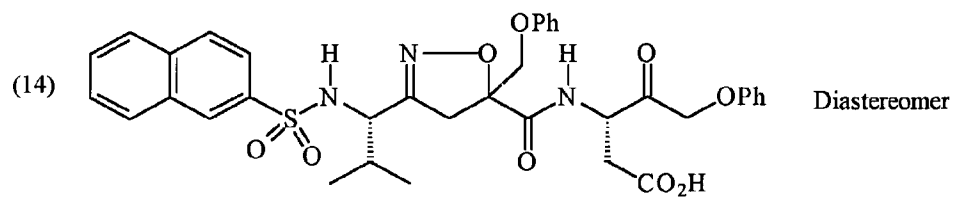
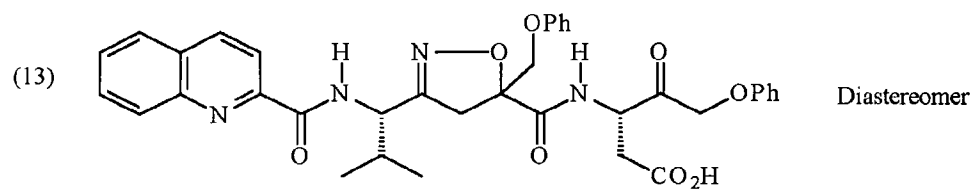
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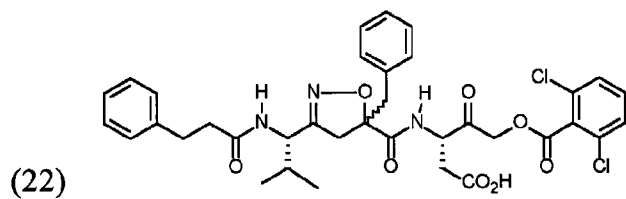
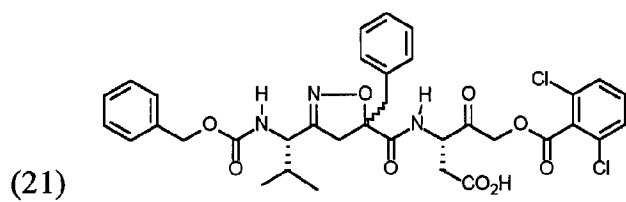
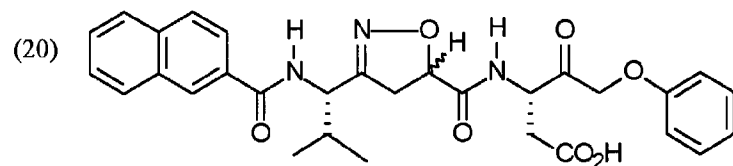
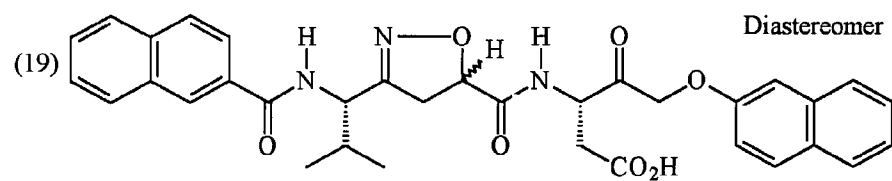
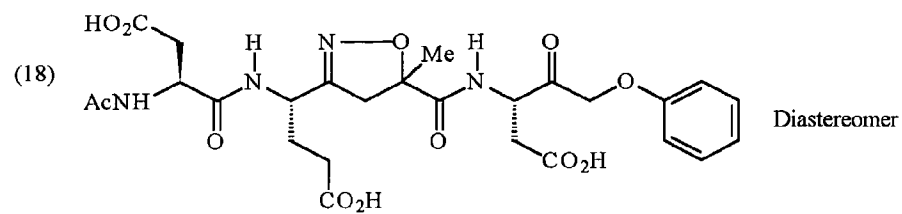
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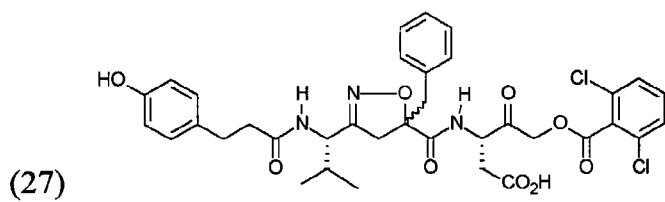
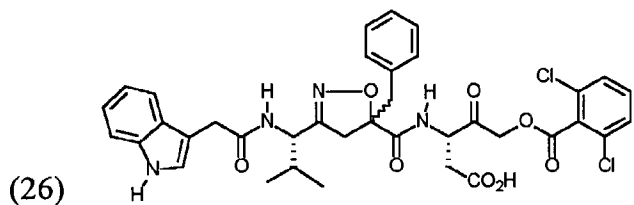
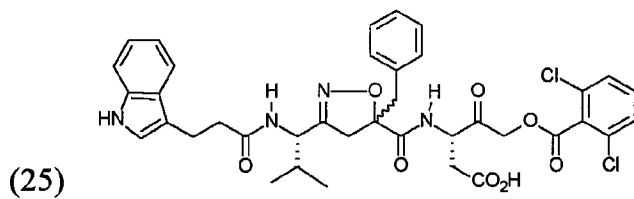
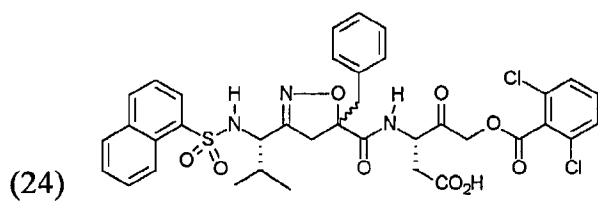
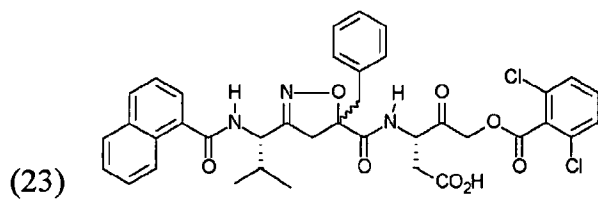
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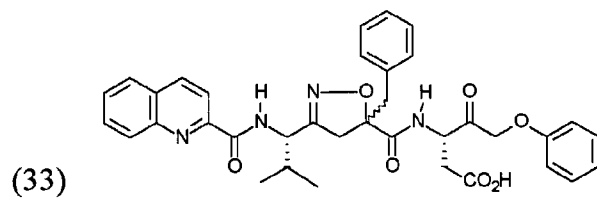
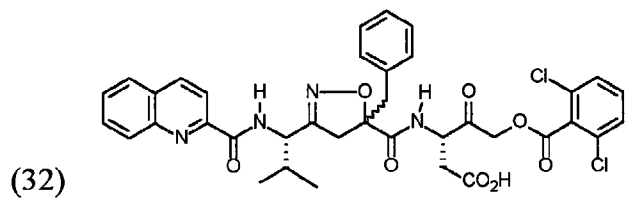
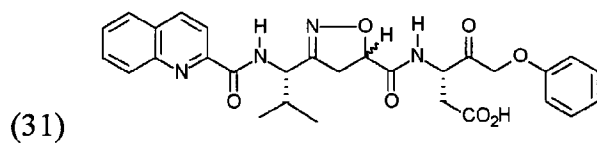
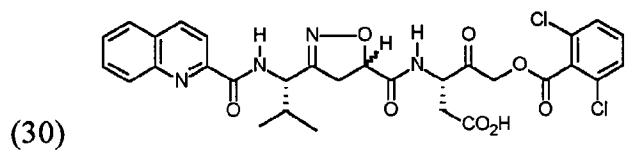
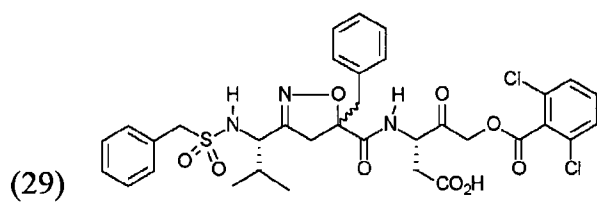
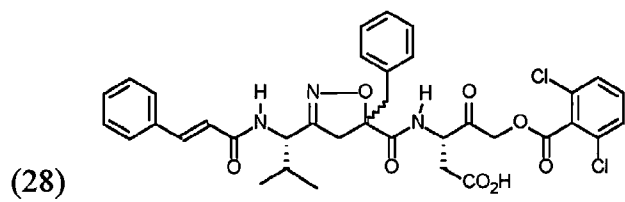
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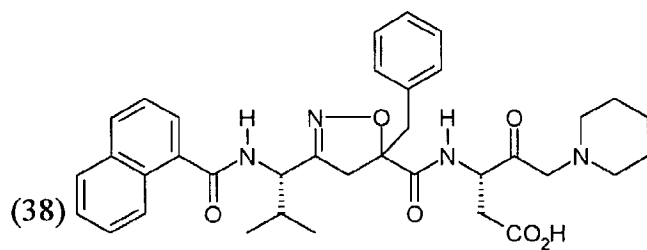
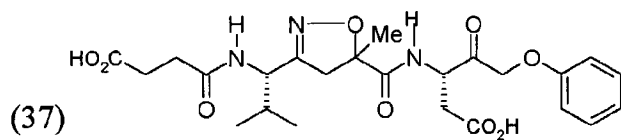
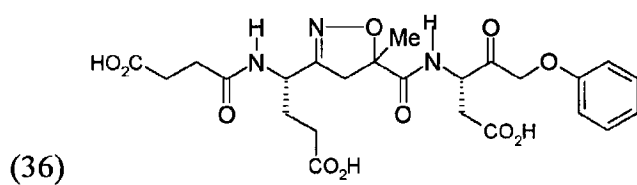
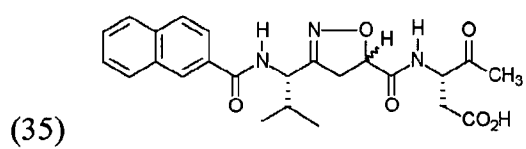
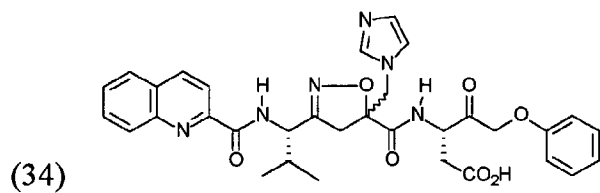
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The isoxazoline derivative of formula (I) and the pharmaceutically

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acceptable salts, the esters, and the isomers thereof have useful pharmacological properties. For example, the derivative of the formula (I) possesses an inhibitory activity for caspases. Due to their pharmacological activity, they can effectively be used as the therapeutics for a number of diseases, such as, for example the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injury by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

The compounds of the present invention therefore may be used as medicines against above-mentioned diseases. Said use as a medicine or method of treatment comprises local or systemic administration to patients of an effective amount of the compounds according to the invention for treating the diseases.

The subject compounds may be formulated into various pharmaceutical forms for administration purposes. Said pharmaceutical forms or compositions are deemed novel and consequently constitute a further aspect of the present invention. Also the preparation of said composition constitutes a further aspect of the present invention. To prepare the pharmaceutical composition of this invention, an effective amount of the compound, in base or salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, percutaneously, or by parenteral injection.

For example, in preparing the composition in oral dosage form, any of the

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usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agent and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the composition suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agents and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment.

It is especially advantageous to formulate the above pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit as used in the specification and claims herein refers to physically discrete units suitable as unitary dosage, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required

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pharmaceutical carrier. Examples of such dosage unit forms are tablets, capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In view of the usefulness of the subject compounds in the treatment of the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation, it is evident that the present invention provides a method of treating the subject suffering from the diseases, said method comprising the local or systemic administration of a pharmaceutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutical carrier. Those skilled in the treatment of the diseases associated could easily determine the effect amount. In general it is contemplated that an effective amount would be from 0.01 mg/kg to 4 mg/kg body weight. However, it is evident to those skilled in the art that such amount ranges are guidelines only and are not intended to limit the scope or use of the invention to any extent.

### **EXAMPLES**

The present invention will be described in greater detail through the following examples. The examples are presented for illustrating purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

(A) Hydroxamoyl chloride synthesis (Examples 1 to 4)

Example 1:        Synthesis of N-t-butoxycarbonyl-(S)-valinal and

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### N-t-butoxy-carbonyl- (S)-valinal oxime

To a solution of dimethyl sulfoxide (11.7 mL, 3.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (~200 mL) under  $\text{N}_2$  at  $-60^\circ\text{C}$  was added slowly oxalyl chloride (5.78 mL, 1.2 eq). After 10 min., a solution of N-t-butoxycarbonyl-(S)-valinol (11.23g, 55.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added slowly, and the flask was rinsed with 20 mL of  $\text{CH}_2\text{Cl}_2$ . The resulting white suspension was stirred for 1h at  $\sim -50^\circ\text{C}$ . The reaction solution was treated with diisopropylethylamine (28.8 mL, 3.0 eq) and stirred for about 20 min. at  $-23^\circ\text{C}$  then diluted with hexanes (400 mL). The mixture was washed with water (150 mL), 1N- $\text{KHSO}_4$  solution (x3, total 1 L), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The yellowish liquid obtained was used directly in next step without further purification.

The crude valinal in ethanol (60 mL)-water (30 mL) at water bath temperature was treated with hydroxylamine hydrochloride (5.76g, 1.5 eq) and  $\text{Na}_2\text{CO}_3$  (4.39g, 0.75 eq.). The reaction generated a lot of solid in 1 min., thus diluted with ethanol-water (1:1, 60 mL) and stirred for 1h. The reaction solution was poured into saturated NaCl (100 mL), then extracted with ethyl acetate twice (300 mL). Organic extracts were washed with sat'd  $\text{NaHCO}_3$  (100mL x 2), dried (anh.  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to yield white powder (11.34g, syn,anti mixture of oximes).

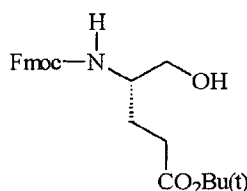
### Example 2: Synthesis of (2S)-2-(t-butoxycarbonyl)amino-1-chloro-3-methyl-butane-1-one oxime

N-t-butoxy-carbonyl-(S)-valinal oxime (11.34g) in DMF (100 mL) was treated with NCS (7.75g) and stirred in warm water bath ( $\sim 40^\circ\text{C}$ ) for 1h. After removal of DMF, the residue was extracted with ethyl

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acetate-hexanes (1:1, 150 mL), washed with water (100 mL x 3), dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give 13.69g of the title compound.

Example 3: Synthesis of 4-(9-fluorenylmethoxycarbonyl)amino-(4S)-5-hydroxy-pentanoic acid t-butyl ester

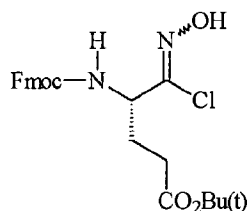


To a solution of N-(9-fluorenylmethoxycarbonyl)- $\gamma$ -t-butyl glutamic acid (8.51g, 20.0 mmol) and NMM (2.42mL, 1.1 eq) in dry THF (110 mL) under N<sub>2</sub> at 0 °C was added isobutyl chloroformate (2.72mL, 1.05eq). After 20 min., the reaction mixture was filter-added to a solution of NaBH<sub>4</sub> (1.5g) in THF (120mL)-MeOH (30 mL) at -78 °C under N<sub>2</sub> and rinsed with dry THF (20mL). After stirring for 2.5h at -78 °C, the reaction was quenched with acetic acid (13mL). After concentrating to ~ 50mL, the residue was dissolved in ethyl acetate-hexanes (200 mL,1:1), washed with water (150 mL x 2). Aqueous layer was reextracted with ethyl acetate-hexanes (150 mL,1:1). Combined extract was washed with sat'd NaHCO<sub>3</sub> (150 mL x 2), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give 8.30g of the title compound as glasslike solid. The crude alcohol was used directly.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (2H, d, J=7.3Hz), 7.66 (2H, d, J = 7.8 Hz), 7.41 (2H, t, J = 7.3 Hz), 7.31 (2H, pseudo t, J = 7.8, 7.3 Hz), 5.18 (NH, d), 4.41 (2H, m), 4.22 (1H, m), 3.72-3.57 (3H, m), 2.33 (2H, m), 1.93-1.77 (2H, m), 1.45(9H, s).

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Example 4: Synthesis of 4-(9-fluorenylmethyloxycarbonyl)amino-(4S)-5-chloro-5- hydroxyimino-pentanoic acid t-butyl ester



To a solution of DMSO (3.0 mL) in dry  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $-65^\circ\text{C}$  under  $\text{N}_2$  was added oxalyl chloride (2.10 mL, 1.2eq) slowly. After 15 min., a solution of 4-(9-fluorenylmethyloxycarbonyl)amino-(4S)-5-hydroxypentanoic acid t-butyl ester (8.30 g, 20 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added and rinsed with dry  $\text{CH}_2\text{Cl}_2$  (20 mL). The resulting solution was stirred for 2h at  $-40 \sim -50^\circ\text{C}$ .  $\text{EtN}(\text{i-Pr})_2$  (10.45 mL, 3.0eq) was added thereto and the reaction solution was slowly warmed up to  $-10^\circ\text{C}$  with TLC checking (conversion to aldehyde is relatively slow,  $\sim 1\text{h}$ ). The reaction mixture was diluted with hexanes (300 mL), washed with water(150 mL), with 1N- $\text{KHSO}_4$  (x 3, total 500 mL), dried with anh.  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give corresponding aldehyde.

The crude aldehyde in ethanol(60 mL)- $\text{CH}_2\text{Cl}_2$  (30 mL)-water(10 mL) at  $0^\circ\text{C}$  was treated with  $\text{H}_2\text{NOH} \cdot \text{HCl}$  (2.08 g, 1.5eq) and  $\text{Na}_2\text{CO}_3$  (1.60g, 0.75 eq). The reaction was stirred at room temperature for 30 min., then water (10 mL) was added and stirred for additional 1h. The reaction was stirred further(1h) with additional  $\text{H}_2\text{NOH} \cdot \text{HCl}$  (400 mg) and  $\text{Na}_2\text{CO}_3$  (320 mg). Most of the volatiles were removed in vacuo, and the residue was taken up with ethyl acetate (200 mL), washed with water(100 mL), sat'd  $\text{NaHCO}_3$  (100 mL), dried (anh.  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to give the desired oxime (8.30g, syn + anti) as white powder.

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The crude oxime in DMF (35 mL) was treated with NCS (2.67g, 20.0 mmol). The reaction was stirred in warm (40°C) bath for 1h. After removal of the DMF in high vacuum rotary evaporator, the residue was taken up with hexane-ethyl acetate (1:1, 150 mL), washed with water (100 mL x 3), dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give the title compound (9.25g, syn + anti).

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.88(1H, s), 7.75(2H, d, J = 7.3Hz), 7.57(2H, m), 7.39(2H, t, J = 7.32Hz), 7.30 (2h, pseudo t, J = 7.8,7.3Hz), 5.46(1H, d), J = 9.3 Hz), 4.63(1H, m), 4.43-4.38(2H, m), 4.19(1H, m), 2.3(2H, m), 2.03(2H, m), 1.43(9H, s). (NMR data reported for major isomer.)

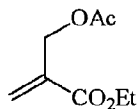
Following compounds were similarly prepared.

- . 1-chloro-3-methyl-(2S)-2-phenylmethyloxycarbonylamino-butane-1-one oxime,
- . 3-(t-butoxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butanoic acid methyl ester,
- . 3-(phenylmethyloxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butanoic acid t-butyl ester, and
- . 3-(9-fluorenylmethyloxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butan oic acid t-butyl ester.

(B) Synthesis of acrylate derivatives (Examples 5 to 8)

Example 5: Synthesis of ethyl 2-acetoxymethylacrylate

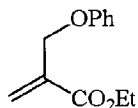
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A solution of ethyl 2-hydroxymethyl acrylate (17.3g, 133 mmol, purity ~ 70%, ref: Villieras, J. and Rambaud, M. *Synthesis*, **1982**, 914) in dry CH<sub>2</sub>Cl<sub>2</sub> (200 mL) under N<sub>2</sub> at 0 °C was treated with acetic anhydride (18.8 mL, 1.5 eq) and triethyl amine (37 mL, 2.0 eq). After overnight stirring at room temperature, the reaction was diluted with hexanes (400 mL), washed with sat'd NaHCO<sub>3</sub> (300 mL x 2), dried (anh Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Simple distillation gave 4.6g of the title compound as clear liquid. NMR analysis showed ~ 70 % purity.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 6.36 (1H, s), 5.84 (1H, s), 4.81(2H, s), 4.25 (2H, q, J = 7.3 Hz), 2.11 (3H, s), 1.31 (3H, t, J = 7.3 Hz)

#### Example 6: Synthesis of ethyl 2-phenoxyethylacrylate



A solution of ethyl 2-bromomethylacrylate (2.00g, 10.4 mmol, ref: Villieras, J. and Rambaud, M. *Synthesis*, **1982**, 914) and phenol(975 mg, 1.0eq) in dry THF (20 mL) under N<sub>2</sub> at 0 °C was treated with anhydrous K<sub>2</sub>CO<sub>3</sub> (1.43g, 1.0 mol eq). No reaction was observed for 1h. Anhydrous DMF (20 mL) was added and stirred for 2h at 0 °C and for 1h at room temperature. After evaporation of DMF, water(100 mL) was added, and the reaction was extracted with ethyl acetate (100 mL x 2). The organic extract was washed with brine (100 mL), dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Flash chromatography (40% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) gave 1.712g

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(80%) of the title compound.

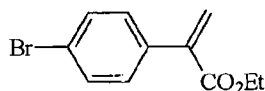
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (2H, yt,  $J = 7.3$  Hz), 6.99-6.96 (3H, m), 6.41 (1H, s), 6.01 (1H, s), 4.78 (2H, s), 4.27 (2H, q,  $J = 7.33$  Hz)

#### Example 7: Synthesis of ethyl 2-benzylacrylate

To a solution of bromobenzene (7.15g, 45.5 mmol) in THF (30mL) was added  $n\text{-BuLi}$  (16.6mL, 2.5M in Hexane, 41.4mmol) under  $\text{N}_2$  at  $-78^\circ\text{C}$ . It was stirred for 10min. To a suspension of  $\text{CuCN}$  (3.71g, 41.4mmol) in THF (30mL) was added lithiated benzene solution via cannula under  $\text{N}_2$  at  $-78^\circ\text{C}$ . The reaction mixture was stirred for another 10 min. at  $-78^\circ\text{C}$  and ethyl 2-bromomethyl acrylate (4.00g, 20.7 mmol) in THF was added. The reaction mixture was warmed up to room temperature slowly and quenched with 2N  $\text{HCl}$ . All precipitates were filtered off and filtrate was diluted with hexanes (400 mL), washed with sat'd  $\text{NaHCO}_3$  (300 mL x 2), dried (anh  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. Flash chromatography (2% ethyl acetate-hexanes) gave 3.04g(77%) of the title compounds .

$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.22 (5H, m), 6.26 (1H, s), 5.48(1H, s), 4.22(2H, q,  $J = 6.3\text{Hz}$ ), 3.66 (2H, s), 1.29 (3H, q,  $J = 6.3$  Hz).

#### Example 8: Synthesis of ethyl 2-(4-bromophenyl)acrylate



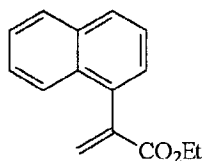
The title compound was prepared following the known procedure (Helvetica Chimica Acta 1986, 69 2048).

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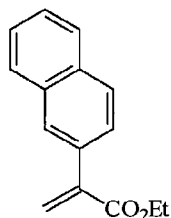
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 (2H, d), 7.29 (2H, d), 6.37 (1H, s), 5.90 (1H, s), 4.29 (2H, q), 1.33 (3H, t)

Following compounds were similarly prepared.

. Ethyl 2-(1-naphthyl)acrylate



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (2H, t,  $J = 7.3$  Hz), 7.44 (1H, d,  $J = 8.8$  Hz), 7.48-7.43 (3H, m), 7.37 (1H, d,  $J = 6.8$  Hz), 6.70 (1H, d,  $J = 2.0$  Hz), 5.89 (1H, d,  $J = 2.0$  Hz), 4.22 (2H, q,  $J = 7.3$  Hz), 1.21 (3H, t,  $J = 7.3$  Hz),



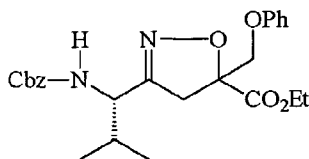
. Ethyl 2-(2-naphthyl)acrylate

$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95 (1H, s), 7.90-7.86 (3H, m), 7.59-7.52 (3H, m), 6.47 (1H, d,  $J = 1.0\text{Hz}$ ), 6.06 (1H, d,  $J = 1.0$  Hz), 4.38 (2H, q,  $J = 6.8$  Hz), 1.40 (3H, t,  $J = 6.8\text{Hz}$ ).

(C) General procedure for isoxazoline synthesis (Examples 9 and 10)

Example 9: Synthesis of 3-((1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl)-5-phenoxyethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

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A solution of (2S)-2-phenylmethyloxycarbonylamino-1-chloro-3-methylbutane-1-one oxime (640 mg, 2.25mmol) and ethyl 2-phenoxyethylacrylate (464mg) in dry ether(10 mL) under N<sub>2</sub> at -78°C was treated with triethylamine (627 uL, 2.0 eq). The reaction was stirred overnight, allowing to warm up to room temperature slowly. Water(100 mL) was added, and the reaction was extracted with ethyl acetate (100 mL x 2), washed with water(100mL), dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Flash chromatography (15% ethyl acetate-hexanes) gave 851mg(83%) of the title compounds as 1:1 mixture of diastereomers.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.34(7H, m), 6.98 (1H, t, J = 7.3Hz), 6.89 (2H, d, J = 7.7Hz), 5.61 (1H, d, J = 9.3 Hz), 5.15-5.08 (2H, m), 4.50 (1H, br s), 4.33-4.22 (4H, m), 3.60-3.54(1H, m), 3.32-3.27(1H, m), 2.10 (1H, m), 1.29 (3H, m), 1.02-0.94 (6H, m).

The following compounds were prepared similarly:

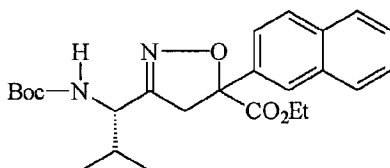
. Ethyl 3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.45-7.15 (m, 10H), 5.07 (m, 2.5H), 4.90 (d, 0.5H), 4.30-4.18 (m, 3H), 3.36-2.88 (m, 4H), 1.95-1.80 (m, 1H), 1.27 (m, 3H), 0.86-0.55 (m, 6H).

. 3-[(1S)-1-t-butoxycarbonylamino-2-methyl-propyl]-5-(2-naphthyl)-4,5-di-

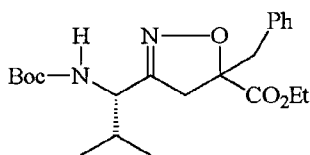
- 45 -

hydro-isoxazole-5-carboxylic acid ethyl ester



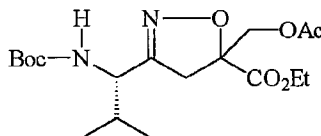
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97(1H, s), 7.86-7.82 (3H, m), 7.52-7.48 (3H, m), 4.93 (1H, br), 4.37 (1H, m), 4.25 -4.18 (2H, m), 4.10-4.05 (1H, two doublets,  $J=17.1$ , 17.6 Hz), 3.28-3.22 (1H, two doublets,  $J = 17.1$ , 17.1 Hz), 2.05 (1H, m), 1.43 ((H, s), 1.24-1.20 (3H, m), 0.98-0.91 (6H, m).

. 3-[(1S)-1-t-butoxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro- i-soxazole-5-carboxylic acid ethyl ester (~1:1 diastereomers)



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (5H, m), 4.82 and 4.60 (1H, two m), 4.25-4.15 (3H, m), 3.38-3.29 (2H, m), 3.10 (1H, m), 2.90 (1H, m), 1.43 and 1.42 (9H, two s), 1.27 (3H, m), 0.90-0.80 (6H, m).

. 5-acetoxymethyl-3-[(1S)-1-t-butoxy-carbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

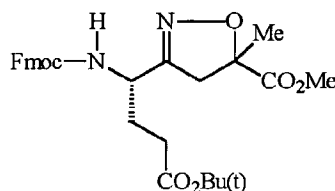


$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.93 (1H, br), 4.44-4.26 (5H, m), 3.50

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(1H, m), 3.10 (1H, m), 2.08 (4H, s + br 1H), 1.46 (9H, s), 1.32-1.30 (3H, m), 1.02-0.96 (6H, m).

Example 10: Synthesis of 3-[(1S)-1-(9-fluorenylmethoxycarbonylamino)-3-t-butoxycarbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester



A solution of 4-(9-fluorenylmethoxycarbonyl)amino-(4S)-5-chloro-5-hydroxy-imino-pentanoic acid t-butyl ester (3.44g, 7.50 mmol) and methyl methacrylate (2.40mL, 3.0 eq) in dry ether under N<sub>2</sub> at -78 °C was treated with EtN(i-Pr)<sub>2</sub> (1.96mL, 1.5eq). Similar treatment as described previously followed by flash chromatography with 25-30% ethyl acetate/hexanes gave 3.46g (89% overall) of the title compound as diastereomeric mixture.

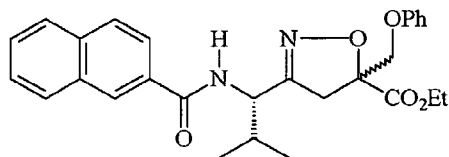
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77 (2H, d, J=7.3Hz), 7.59 (2H, d, J =7.3Hz), 7.40 (2H, t, J = 7.3Hz), 7.31 (2H, t, J =7.3 Hz), 5.34 (1H, m), 4.58-4.38 (3H, m), 4.21 (1H, m), 3.78 (3H, s), 3.48 (1H, m), 2.90-2.81 (1H, m), 2.42-2.27 (2H, m), 2.18 (1H, m), 1.93 (1H, m), 1.63 (3H, s), 1.45 (9H, s)

(D) Transformations of isoxazolines (Deprotection, Introduction of P<sub>4</sub> group, Hydrolysis of ester group) (Examples 11 and 12)

Example 11: Synthesis of 3-{2-methyl- (1S)-1-(naphthalene-2-carbonyl-

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amino)-propyl}-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester



A solution of 3-((1S)-1-(t-butoxycarbonylamino)-2-methyl-propyl)-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (2.00g, 4.76 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $0^\circ\text{C}$  under  $\text{N}_2$  was treated with TFA (6 mL) and stirred for 1.5h. After removal of volatiles, the residue was taken up with ethyl acetate (200 mL), washed with sat'd  $\text{NaHCO}_3$  (100 mL x 2), dried (anh  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. To a solution of the crude product, EDC (1.09g, 1.2 eq), 2-naphthoic acid (983 mg, 1.2 eq) and HOBt (771 mg, 1.2 eq) in DMF (20 mL) at  $0^\circ\text{C}$  was added triethylamine (663  $\mu\text{L}$ , 1.0 eq). The reaction was stirred overnight at room temperature. After removal of volatiles in vacuo, the residue was taken up with ethyl acetate (250 mL), washed with water (100 mL), sat'd  $\text{NaHCO}_3$  (100 mL x 2), dried (anh  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. Flash chromatography with 25-33% ethyl acetate/hexanes gave 2.04g (90%) of the title compound.

$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (1H, s), 7.93-7.84 (4H, m), 7.58-7.52 (2H, m), 7.29-7.22 (2H, m), 7.00-6.81 (4H, m), 5.06-5.01 (1H, m), 4.36-4.24 (4H, m), 3.68-3.61 (1H, m), 3.43-3.39 (1H, m), 2.28 (1H, m), 1.31-1.26 (3H, m), 1.12-1.05 (6H, m).

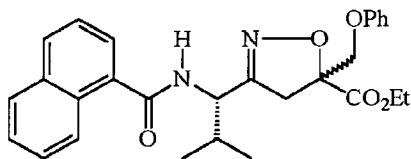
Hydrolysis of isoxazoline 5-carboxylic acid ester: The above compound (2.04g) in distilled THF (40 mL) (not completely soluble) was treated with 1N- $\text{NaOH}$  (5.2 mL, 1.2 eq). After 4h (~50% completion), additional

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1N-NaOH (1.0 mL) was added. After overnight stirring, the reaction was neutralized with concentrated 1N-HCl. The residue was taken up with  $\text{CH}_2\text{Cl}_2$  (>700 mL), washed with water, dried (anh  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to give 1.948g (103%) of the free carboxylic acid, which was used directly in next step.

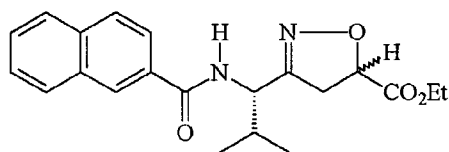
The following compounds were prepared similarly:

. 3-{2-methyl-(1S)-1-(naphthalene-1-carboxylamino)-propyl}-5-phenoxyethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (1H, d,  $J = 8.3$  Hz), 7.93-7.86 (2H, m), 7.66 (1H, m), 7.54-7.42 (3H, m), 7.29-7.25 (2H, m), 7.00-6.90 (3H, m), 6.49 (1H, m), 5.13-5.09 (1H, m), 4.40-4.26 (4H, m), 3.69-3.64 (1H, m), 3.44-3.41 (1H, m), 2.28 (1H, m), 1.32-1.01 (9H, m).

. 3-{2-methyl-(1S)-1-(naphthalene-2-carboxylamino)-propyl}-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (1H, s), 7.94-7.83 (4H, m), 7.59-7.53 (2H, m), 6.80-6.70 (NH, two d), 5.07-5.03 (2H, m), 4.28-4.21 (2H, m), 3.37-3.33 (2H, m), 2.28 (1H, m), 1.34-1.25 (3H, m), 1.12-1.02 (6H, m).

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. 3-[(1S)-1-(1-naphthalenecarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (d,  $J = 7.8$  Hz, 1H), 7.94-7.86 (m, 2H), 7.61-7.11 (m, 9H), 6.36 (d,  $J = 9.3$  Hz, 0.5H), 6.09 (d,  $J = 9.3$  Hz, 0.5H), 4.94-4.85 (m, 1H), 4.27-4.21 (m, 2H), 3.49-2.98 (m, 4H), 2.15 & 1.97 (two m, 1H), 1.30-1.26 (m, 3H), 1.03-0.59 (m, 6H).

. Ethyl 3-[(1S)-1-phenethylcarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric)

$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28-7.17 (m, 10H), 5.74 & 5.50 (two d,  $J = 9.3$  Hz, NH), 4.58-4.52 (m, 1H), 4.24-4.20 (m, 2H), 3.34-3.25 (m, 2H), 3.11-2.82 (m, 4H), 2.52-2.45 (m, 2H), 1.93 & 1.75 (two m, 1H), 1.29-1.25 (m, 3H), 0.79-0.41 (m, 6H).

. 3-[(1S)-1-(1-naphthalenesulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68-8.64 (m, 1H), 8.29-8.25 (m, 1H), 8.07 (m, 1H), 7.93 (m, 1H), 7.71-7.52 (m, 3H), 7.23-6.98 (m, 5H), 5.27 & 5.19 (two m, 1H), 4.12-4.07 (m, 2H), 3.75 & 3.66 (two m, 1H), 3.16-2.43 (m, 4H), 1.77-1.62 (m, 1H), 1.25-1.16 (m, 3H), 0.86-0.57 (m, 6H).

. 3-[(1S)-1-(indole-3-yl-ethylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

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<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.16-8.12 (m, 1H), 7.62-7.56 (m, 1H), 7.36-6.94 (m, 9H), 5.71 (d, J = 9.3 Hz, 0.5H), 5.42 (d, J = 8.8 Hz, 0.5H), 4.56-4.50 (m, 1H), 4.25-4.17 (m, 2H), 3.30-2.51 (m, 8H), 1.89-1.70 (m, 1H), 1.28-1.24 (m, 3H), 0.73-0.41 (m, 6H).

. 3-[(1S)-1-(indole-3-yl-methylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5 -dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.56 & 8.52 (two br s, 1H), 7.55-7.05 (m, 10H), 5.98-5.91 (m, 1H), 4.57 (m, 1H), 4.22-4.15 (m, 2H), 3.73 (m, 2H), 3.28-2.79 (m, 4H), 1.87-1.68 (m, 1H), 1.27-1.20 (m, 3H), 0.75-0.34 (m, 6H).

. 3-[(1S)-1-(cinnamoylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.61-7.23 (m, 11H), 6.40-6.34 (m, 1H), 6.06 (d, J = 8.8 Hz, 0.5H), 5.81 (d, J = 9.3 Hz, 0.5H), 4.76-4.69 (m, 1H), 4.26-4.19 (m, 2H), 3.42-2.94 (m, 4H), 2.06 & 1.88 (two m, 1H), 1.28-1.24 (m, 3H), 0.93-0.57 (m, 6H).

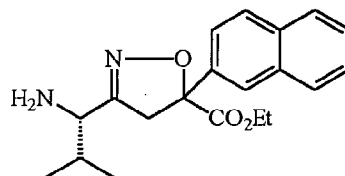
. 3-[(1S)-1-(phenylmethylsulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.35-7.16 (m, 10H), 4.66-4.61 (m, 1H), 4.25 (m, 2H), 4.11-3.84 (m, 3H), 3.71-2.82 (m, 4H), 1.80 & 1.70 (two m, 1H), 1.28 (m, 3H), 0.85-0.58 (m, 6H).

. 3-[2-methyl-(1S)-1-amino-propyl]-5-(2-naphthyl)-4,5-dihydro-isoxazole-5-car

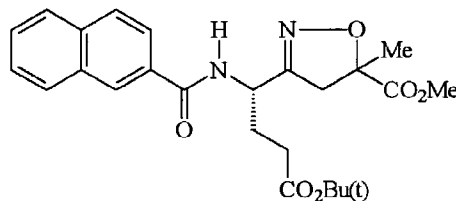
- 51 -

boxylic acid ethyl ester (~1.3:1 diastereomers)



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (1H, s), 7.86-7.82 (3H, m), 7.53-7.49 (3H, m), 4.25-4.02 (3H, m), 3.55-3.48 (1H, two d,  $J = 7.3, 6.8\text{Hz}$ ), 3.35 (0.45H, d,  $J=17.1\text{ Hz}$ ), 3.19 (0.55H, d,  $J = 17.1\text{Hz}$ ), 1.78 (1H, m), 1.22 (3H, t,  $J = 7.3\text{ Hz}$ ), 0.96-0.82 (6H, m)

Example 12: Synthesis of 3-[(1S)-1-(2-naphthoylamino)-3-t-butoxycarbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester



A solution of 3-[(1S)-1-(9-fluorenylmethyloxycarbonylamino)-3-t-butoxycarbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (440mg, 0.842 mmol) in DMF (8.0 mL) at room temperature was treated with piperidine (2.5 mL) for 5 min. After concentration, the residue was dissolved in DMF (10 mL), and treated with 2-naphthoic acid (174 mg, 1.2 eq), EDC (210 mg, 1.3 eq), HOBt (148 mg, 1.3 eq) and triethylamine (0.35 mL, 3.0 eq), then stirred overnight ( $0^\circ\text{C}$  to room temperature). Usual workup followed by chromatography gave 133 mg of the title compound and 260 mg (~50% purity) mixture.

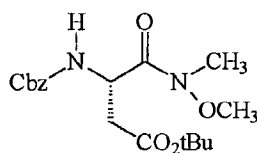
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (1H, s), 7.92-7.83 (4H, m), 7.58-7.48

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(2H, m), 7.34 (1H, d, J=7.8Hz), 5.04 (1H, m), 3.78 and 3.74 (3H, two s), 3.62-3.53 (1H, two d, J=17.1, 17.6Hz), 3.00-2.96 (1H, two d, J =17.1, 17.6 Hz), 2.56-2.08 (4H, m), 1.63 and 1.59 (3H, two s), 1.41 and 1.40 (9H, two s)

(E) Synthesis of aspartic acid derivatives (Examples 13 to 18)

Example 13: Synthesis of N-phenylmethyloxycarbonyl- $\beta$ -t-butyl aspartic acid (N-methoxy) methyl amide

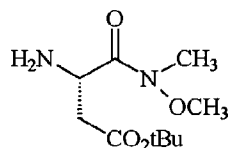


A solution of N-benzyloxycarbonyl- $\beta$ -t-butyl aspartic acid (2.0g, 6.2 mmol), N,O-dimethylhydroxylamine hydrochloride (724 mg, 1.2 eq) and HOBt (1.00g, 1.2 eq) in DMF (20 mL) at 0°C was treated with EDC (1.42g, 1.2 eq) and triethylamine (1.29 mL, 1.5 eq). After overnight stirring (0°C to room temperature), the reaction was diluted with water (100mL), extracted with ethyl acetate-hexanes (1:1, 100 mL x 2), washed with water (100 mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Flash chromatography with ethyl acetate-hexanes (3:7) gave 2.039g (90%) of the title compound.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36-7.31 (5H, m), 5.70 (1H, br), 5.16-5.08 (3H, m), 3.80 (3H, s), 3.23 (3H, s), 2.74-2.71 (1H, m), 2.59-2.57 (1H, m), 1.43 (9H, s).

Example 14: Synthesis of  $\beta$ -t-butyl aspartic acid N,O-dimethylhydroxylamine amide

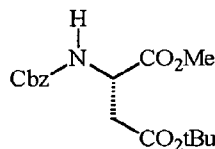
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Conventional hydrogenolysis of N-phenylmethyloxycarbonyl- $\beta$ -t-butyl aspartic acid (N-methoxy)methyl amide ( $H_2$  balloon, 10% Pd/C, EtOH) gave the title compound (100%).

$^1H$ -NMR (500 MHz,  $CDCl_3$ )  $\delta$  4.13 (1H, m), 3.77 (3H, s), 3.22 (3H, s), 2.71-2.67 (1H, m), 2.42-2.38 (1H, m), 1.46 (9H, s)

Example 15: Synthesis of N-phenylmethyloxycarbonyl- $\beta$ -t-butyl aspartic acid methyl ester



Treatment of N-benzyloxycarbonyl- $\beta$ -t-butyl aspartic acid with diazomethane/ ether gave the desired methyl ester (100%).

$^1H$ -NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.35-7.27 (5H, m), 5.75 (1H, d), 5.13 (2H, s), 4.60 (1H, m), 3.75 (3H, m), 2.90 (1H, m), 2.76 (1H, m), 1.42 (9H, s).

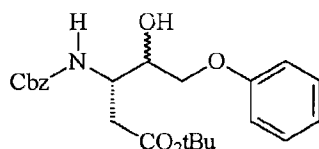
Example 16: Synthesis of  $\beta$ -t-butyl aspartic acid methyl ester hydrochloride

Conventional hydrogenolysis of N-phenylmethyloxycarbonyl- $\beta$ -t-butyl

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aspartic acid methyl ester ( $H_2$  balloon, 10% Pd/C, EtOH-HCl) gave the desired product as hydrochloride salt.

Example 17: Synthesis of (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester



A solution of N-phenylmethyloxycarbonyl- $\beta$ -t-butyl-aspartic acid (5.03g, 15.6 mmol), NMM (1.90 mL, 17.1 mmol) in dry THF (60 mL) under  $N_2$  at  $-15^\circ C$  was treated with isobutyl chloroformate (2.12 mL, 16.3 mmol) and the resulting suspension was stirred for 20 min. To the mixture at  $0^\circ C$  was added dry diazomethane/ether (synthesized from 2.0 eq of 1-methyl-3-nitro-1-nitroso-guanidine, 60 mL) and stirred for 30 min. When the diazo ketone synthesis was completed (TLC analysis), 30% HBr/AcOH (6.42 mL, 2.0 eq) was introduced thereto (stirred for 30-60 min.) at  $0^\circ C$ . The reaction was extracted with ethyl acetate, washed with sat'd  $NaHCO_3$  (x 2), brine, dried (anh.  $Na_2SO_4$ ), filtered and concentrated to give bromomethyl ketone derivative (6.4g).

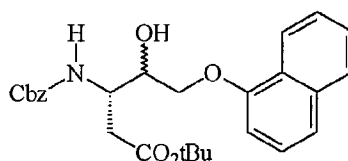
The bromomethyl ketone (4.36g) and phenol (1.13g, 1.1 eq) in DMF (18 mL) at room temperature was treated with freshly dried KF (1.58g, 2.5 eq) and stirred for 2 h. Usual extractive workup gave crude phenoxy ketone. The crude phenoxy ketone in methanol (20 mL) at  $-78^\circ C$  was treated with  $NaBH_4$  (412 mg) in MeOH (40 mL) ( $78^\circ C$  to room temperature, 2h). The reaction was quenched with acetic acid. Usual extractive workup followed by flash chromatography (ethyl acetate-hexanes = 1:5) gave 2.58g (57%) of the title compound as diastereomeric mixture.

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$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.26 (7H, m), 6.98-6.87 (3H, m), 5.71-5.53 (NH, two d), 5.10 (2H, s), 4.24-3.92 (4H, m), 2.70-2.63 (2H, m), 1.44 and 1.43 (9H, two s).

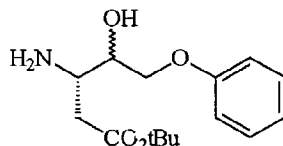
Following compound was prepared similarly:

. (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-(1-naphthyl)oxy-pentanoic acid t-butyl ester



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (1H, m), 7.80 (1H, m), 7.50-7.33 (9H, m), 6.80 (1H, m), 5.73 and 5.55 (1H, two d,  $J = 8.3$  Hz), 5.10 (2H, s), 4.30-4.15 (4H, m), 2.76-2.69 (2H, m), 1.44 (9H, s).

Example 18: Synthesis of (3S)-3-amino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester



Conventional hydrogenolysis of (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester ( $\text{H}_2$  balloon, Pd/C, EtOH) gave the desired product (100%).

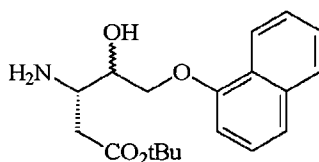
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.26 (2H, m), 6.97-6.90 (3H, m),

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4.08-3.82 (3H, m), 3.43 (1H, m), 2.63-2.37 (2H+NH<sub>2</sub>+OH, m), 1.46 and 1.45 (9H, two s).

The following compound was prepared similarly:

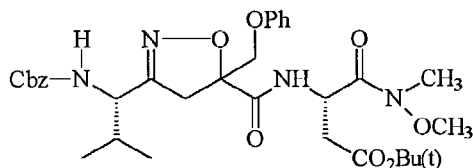
. (3S)-3-amino-4-hydroxy-5-(1-naphthyl)oxy-pentanoic acid t-butyl ester



<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.22 (1H, m), 7.80 (1H, m), 7.50-7.34 (4H, m), 6.84 (1H, m), 4.26-4.20 (2H, m), 4.03-3.94 (1H, m), 3.51 (1H, m), 2.70-2.40 (2H, m), 1.47 and 1.46 (9H, two s).

(F) Coupling of isoxazoline derivatives and aspartic acid derivatives and further transformations thereof (Examples 19 to 24).

Example 19: Synthesis of (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide



A solution of 3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (502mg, 1.10 mmol) in THF (6.6 mL) was treated with 1N-NaOH (1.33mL). After stirring for 2.5h at room temperature, the reaction was quenched with

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1N-HCl (1.33 mL), then concentrated in vacuo. The residue together with sat'd NaCl(50 mL+ 2-3 mL of 1N-HCl) was extracted with ethyl acetate (100 mL x 2), dried (anh Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give 476mg (101 %) of 3-[(1S)-1-phenylmethyl-oxycarbonylamino-2-methyl-propyl]-5-phenoxyethyl-4,5-dihydro-isoxazole-5-carboxylic acid.

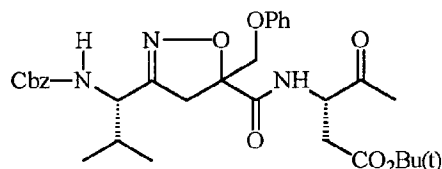
The crude acid (320 mg, 0.75 mmol) and  $\beta$ -t-butyl aspartic acid N-methyl- (N-methoxy) amide (209 mg, 1.2 eq) in DMF (5mL) at 0°C was treated with HOBt (122mg, 1.2 eq), EDC (172mg, 1.2 eq) and triethylamine (0.31 mL, 3.0 eq) and stirred for 3h (0°C to room temperature). Concentration, conventional workup followed by flash chromatography gave less polar isomer (160mg) and more polar isomer (213mg, 33%).

More polar isomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.64 (1H, d), 7.35-7.24 (7H, m), 6.95 (1H, t, J = 7.3 Hz), 6.88 (2H, d, J = 7.8 Hz), 5.55 (1H, d), 5.18-5.08 (3H, m), 4.44 (1H, m), 4.32-4.25 (2H, m), 3.75 (3H, s), 3.32-3.25 (2H, m), 3.12 (3H, s), 2.77-2.71(1H, m), 2.62-2.56 (1H, m), 2.12 (1H, m), 1.44 (9H, s), 1.03-0.91 (6H, m).

Less polar isomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (1H, d, J = 8.3 Hz), 7.36-7.23 (7H, m), 6.95 (1H, t, J = 7.3 Hz), 6.88 (2H, d, J = 8.3 Hz), 5.19-5.11 (4H, m), 4.46 (1H, m), 4.33-4.22 (2H, ABq, J = 10.3 Hz), 3.75 (3H, s), 3.33 (2H, s), 3.23 (3H, s), 2.73 (1H, m), 2.57 (1H, m), 2.07 (1H, m), 1.43 (9H, s), 1.03-0.92 (6H, m).

Example 20: Synthesis of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxyethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid t-butyl ester

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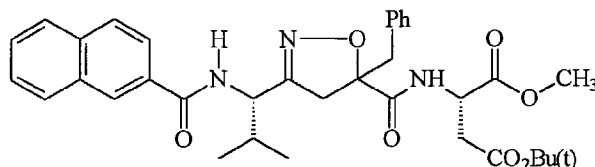
The title compound was obtained from treatment of excess MeMgBr (3.0M in ether, > 3.0 eq) to a solution of less polar isomer of (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxa-zole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide (110 mg, 0.17 mmol) in THF (5 mL) + LiCl satuated THF (2 mL) at 0°C - room temperature (44mg, 43%).

From less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (1H, d,  $J = 9.3$  Hz), 7.36-7.24 (7H, m), 6.96 (1H, t,  $J = 7.2$  Hz), 6.87 (2H, d,  $J = 8.3$  Hz), 5.26 (1H, d,  $J = 8.8$  Hz), 5.12-5.09 (2H, m), 4.66 (1H, m), 4.43 (1H, d,  $J = 9.8$  Hz), 4.21 (1H, d,  $J = 9.8$  Hz), 3.37-3.19 (2H, ABq,  $J = 18.0$  Hz), 2.88 (1H, m), 2.58 (1H, m), 2.25 (3H, s), 2.03 (1H, m), 1.42 (9H, s), 0.99-0.89 (6H, m).

Similar treatment of more polar isomer of (2S)-2-{3-[(1S)-1-phenylmethyloxy-carbonylamino-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide (135 mg) gave 52mg (41%) of the corresponding methyl ketone.

Example 21: Synthesis of (2S)-2-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

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A solution of 3-[2-methyl-(1S)-1-(naphthalene-2-carboxylamino)-propyl]-5-phenyl- methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2.14g, 5.07 mmol), aspartic acid  $\beta$ -t-butyl ester methyl ester hydrochloride (1.46g, 1.2 eq), EDC (1.17g, 1.2 eq) and HOBt (822 mg, 1.2 eq) in DMF (19 mL) was treated with triethylamine (2.12 mL, 3.0 eq), and stirred overnight. Conventional workup followed by flash chromatography (40-50% ethyl acetate-hexanes) gave the title compound (2.94g, 94%) as a white foam.

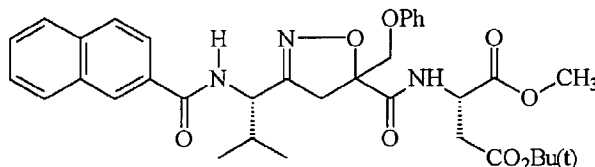
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 and 8.25 (1H, two s), 7.96-7.79 (4H, m), 7.65-7.54 (3H, m), 7.31-7.18 (5H, m), 6.76 (0.5H, d,  $J = 9.3$  Hz), 6.43 (0.5H, d,  $J = 8.8$  Hz), 4.96-4.70 (2H, m), 3.71 and 3.60 (3H, two s), 3.45-3.14 (4H, m), 3.08-2.34 (2H, m), 2.15 (1H, m), 1.47 and 1.44 (9H, two s), 1.04-0.88 (6H, m).

The above compound was hydrolyzed following previously described method (1N-NaOH in THF) to obtain corresponding carboxylic acid (100%).

The following esters and free carboxylic acids were prepared similarly.

. (2S)-2-{3-[2-methyl-(1S)-1-(naphthalene-2-carboxylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

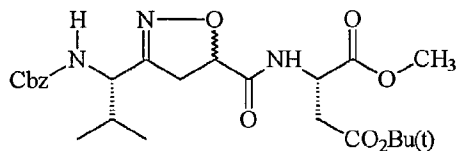
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$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 and 8.30 (1H, two s), 7.95-7.74 (5H, m), 7.59-7.53 (2H, m), 7.28-7.22 (2H, m), 6.99-6.89 (3.5H, m), 6.71 (0.5H, d,  $J = 8.8$  Hz), 5.08-5.01 (1H, m), 4.83-4.79 (1H, m), 4.39-4.29 (2H, m), 3.76 and 3.64 (3H, two s), 3.44 (2H, s), 2.97-2.93 (1H, m), 2.74-2.69 (1H, m), 2.34-2.23 (1H, m), 1.45 and 1.42 (9H, two s), 1.15-1.01 (6H, m).

Hydrolysis of above compound gave free carboxylic acid.

. (2S)-2-{3-[(1S)-1-(phenylmethyloxycarbonyl)-amino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59-7.49 (1H, m), 7.38-7.32 (5H, m), 5.25-4.95 (4H, m), 4.86 (1H, m), 4.48 (1H, m), 3.76 and 3.67 (3H, two s), 3.29 (2H, m), 2.92 (1H, m), 2.71-2.62 (1H, m), 2.04 (1H, m), 1.48 (9H, s), 1.01-0.85 (6H, m)

. (2S)-2-{3-[(1S)-1-phenethylcarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

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<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.56 (d, J = 8.3 Hz, 0.5H), 7.47 (d, J = 9.3 Hz, 0.5 H), 7.28-7.18 (m, 10H), 5.83 & 5.44 (two d, J = 8.8 Hz, 1H), 4.70-4.52 (m, 2H), 3.68 & 3.65 (two s, 3H), 3.33-2.28 (m, 10H), 1.89 (m, 1H), 1.43 & 1.42 (two s, 9H), 0.79-0.63 (m, 6H).

. (2S)-2-{3-[(1S)-1-(1-naphthalenecarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.27 (m, 1H), 7.92-7.85 (m, 2H), 7.61-7.15 (m, 10H), 6.45 & 6.05 (two d, NH), 4.99-4.85 (m, 1H), 4.70 (m, 1H), 3.69 & 3.52 (two s, 3H), 3.50-2.32 (m, 6H), 2.12 (m, 1H), 1.40 & 1.39 (two s, 9H), 1.05-0.80 (m, 6H).

. (2S)-2-{3-[(1S)-1-(1-naphthalenesulfonylamino-2-methyl-propyl)-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino]-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.69-8.62 (m, 1H), 8.33-7.94 (m, 3H), 7.70-7.47 (m, 3H), 7.20-7.05 (m, 5H), 5.32 & 5.15 (two m, 1H), 4.68 & 4.54 (two m, 1H), 3.85 & 3.59 (two m, 1H), 3.82 & 3.62 (two s, 3H), 3.23-1.75 (m, 7H), 1.40 & 1.34 (two s, 9H), 0.85-0.48 (m, 6H).

. (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.53-7.49 (two d, 1H), 7.35-7.25 (m,

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10H), 5.09-5.07 (m, 2.5 H), 4.88 (d, 0.5 H), 4.69 (m, 1H), 4.34 & 4.23 (two m, 1H), 3.68 & 3.63 (two s, 3H), 3.36-2.23 (m, 6H), 1.89 & 1.70 (two m, 1H), 1.42 & 1.40 (two s, 9H), 0.88-0.73 (m, 6H).

. (2S)-2-{3-[(1S)-1-(indole-3-yl-ethylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.54 & 8.38 (two br s, 1H), 7.62-6.97 (m, 1H), 5.83 (d, J = 8.8 Hz, 0.5H), 5.20 (d, J = 9.3 Hz, 0.5H), 4.73-4.69 (m, 1H), 4.61 & 4.48 (two m, 1H), 3.71 & 3.59 (two s, 3H), 3.28-2.26 (m, 10H), 1.87-1.75 (m, 1H), 1.43 & 1.42 (two s, 9H), 0.78-0.50 (m, 6H).

. (2S)-2-{3-[(1S)-1-(indole-3-yl-methylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl-ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.37 & 8.26 (two br s, 1H), 7.54-7.12 (m, 11H), 5.95 (d, J = 8.8 Hz, 0.5H), 5.76 (d, J = 1.5 Hz, 0.5H), 4.68-4.51 (m, 2H), 3.78-3.68 (m, 2H), 3.66 & 3.62 (two s, 3H), 3.28-2.21 (m, 6H), 1.80 (m, 1H), 1.41 & 1.37 (two s, 9H), 0.75-0.46 (m, 6H).

. (2S)-2-{3-[(1S)-1-(cinnamoylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.63-7.25 (m, 12H), 6.43-6.32 (two d, J = 15.6 Hz, 1H), 6.09 & 5.68 (two d, J = 9.3 Hz, 1H), 4.78-4.70 (m, 1H),

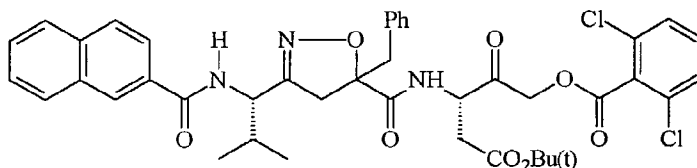
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3.69 & 3.68 (two s, 3H), 3.35-2.31 (m, 6H), 2.03 (m, 1H), 1.43 & 1.40 (two s, 9H), 0.92-0.76 (m, 6H).

. (2S)-2-{3-[(1S)-1-(phenylmethylsulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.67 & 7.60 (two d, J = 8.8 Hz, 1H), 7.40-7.17 (m, 10H), 3.71 & 3.55 (two s, 3H), 3.37-2.23 (m, 6H), 1.70 (m, 1H), 1.42 & 1.47 (two s, 9H), 0.91-0.65 (m, 6H).

Example 22: Synthesis of (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester



A solution of (2S)-2-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-5-phenylmethyl-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester (2.86g, 4.75 mmol) and NMM (0.57 mL, 1.1 eq) in dry THF (x mL) under N<sub>2</sub> at 0°C was treated with isobutyl chloroformate (0.65 mL, 1.05eq), and stirred for 20 min. To the solution at 0°C was added diazomethane, and stirred for 30 min. (TLC analysis). Additional diazomethane was needed to complete the reaction(1h). After completion of the diazoketone formation, 30% HBr/AcOH (4.0 mL, 4.0 eq) was added at 0 oC and the reaction was stirred for 1h. The reaction was extracted with ethyl acetate (x2) and the organic layer was washed with water, sat'd

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NaHCO<sub>3</sub> and brine, dried (anh Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give 3.36g of yellow solid. Half of the solid (~2.375 mmol) was reacted with anhydrous KF (345 mg, 2.5 eq) and 2,6-dichlorobenzoic acid (545 mg, 1.2 eq) in DMF (10 mL) under N<sub>2</sub> at room temperature. Usual workup followed by flash chromatography gave the title compound as diastereomeric mixture (1.53g). Preparative HPLC (38% EtOAc/Hexane) gave less polar diastereomer (585 mg) and more polar diastereomer (358mg).

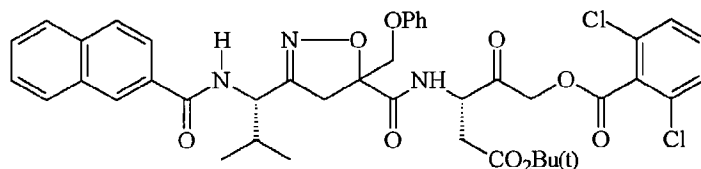
Less polar diastereomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.28 (1H, s), 7.84-7.80 (4H, m), 7.55-7.46 (9H, m), 7.29-7.24 (9H, m), 6.87 (1H, d, J = 8.8 Hz), 5.05-4.93 (3H, m), 4.73 (1H, m), 3.54 (1H, d, J = 18.1 Hz), 3.34 (1H, d, J = 13.7 Hz), 3.19 (1H, d, J = 14.2 Hz), 3.11 (1H, d, J = 17.6 Hz), 2.74-2.70 (1H, m), 2.29-2.24 (2H, m), 1.39 (9H, s), 1.02 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.8 Hz).

More polar diastereomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.28 (1H, s), 7.97-7.75 (5H, m), 7.62-7.57 (2H, m), 7.37-7.22 (8H, m), 6.56 (1H, d, J = 8.3 Hz), 4.94 (1H, m), 4.78 (1H, m), 4.51-4.42 (2H, m), 3.51-3.43 (2H, m), 3.24-3.15 (2H, m), 2.99-2.95 (1H, m), 2.56-2.52 (1H, m), 2.18 (1H, m), 1.45 (9H, s), 1.02 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.4 Hz).

The following compounds were prepared similarly.

. (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester

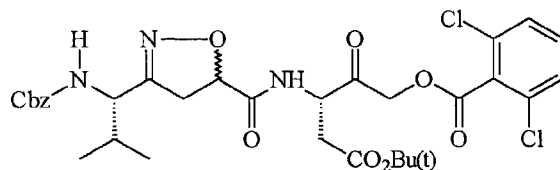
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Less polar diastereomer :  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (1H, s), 7.85-7.81 (5H, m), 7.54-7.46 (2H, m), 7.31-7.23 (5H, m), 6.98-6.87 (4H, m), 5.13-5.03 (3H, m), 4.90 (1H, m), 4.39-4.27 (2H, ABq,  $J = 9.3$  Hz), 3.51 (1H, d,  $J = 17.6$  Hz), 3.41 (1H, d,  $J = 17.6$  Hz), 2.94-2.78 (2H, m), 2.38 (1H, m), 1.41 (9H, s), 1.12-1.08 (6H, two d,  $J = 6.4$  Hz).

More polar diastereomer :  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (1H, s), 8.11 (1H, d,  $J = 8.8$  Hz), 7.93-7.83 (4H, m), 7.59-7.53 (2H, m), 7.33-7.22 (5H, m), 6.97-6.91 (3H, m), 6.77 (1H, d,  $J = 8.8$  Hz), 5.37 (1H, d,  $J = 17.1$  Hz), 5.16 (1H, d,  $J = 17.1$  Hz), 5.01-4.95 (2H, m), 4.53 (1H, d,  $J = 9.8$  Hz), 4.25 (1H, d,  $J = 9.8$  Hz), 3.50 (1H, d,  $J = 7.6$  Hz), 3.32 (1H, d,  $J = 7.6$  Hz), 3.04-3.00 (1H, dd,  $J = 17.1, 4.9$  Hz), 2.73-2.68 (1H, dd,  $J = 17.1, 5.4$  Hz), 2.24 (1H, m), 1.47 (9H, s), 1.10-1.03 (6H, two d,  $J = 6.4$  Hz).

. (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-*t*-butyl ester (diastereomeric mixture)



$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72-7.60 (1H, m), 7.37-7.30 (8H, m), 5.40 (0.5H, d), 5.23-4.85 (6.5H, m), 4.40 (1H, m), 3.30 (2H, m), 2.92-2.65

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(2H, m), 2.10-1.98 (1H, m), 1.44 (9H, s), 1.00-0.87 (6H, m).

Following compounds were similarly prepared:

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.59 (d,  $J = 8.7$  Hz, 1H), 8.31 (d,  $J = 8.3$  Hz, 1H), 8.26 (d,  $J = 8.7$  Hz, 1H), 8.13 (d,  $J = 8.7$  Hz, 1H), 7.98 (d,  $J = 8.7$  Hz, 1H), 7.88 (d,  $J = 7.8$  Hz, 1H), 7.78 (m, 1H), 7.63 (m, 1H), 7.22-7.15 (m, 4H), 6.96-6.81 (m, 6H), 4.99-4.81 (m, 4H), 4.40 (d,  $J = 10.1$  Hz, 1H), 4.21 (d,  $J = 10.0$  Hz, 1H), 3.44 (d,  $J = 17.9$  Hz, 1H), 3.24 (d,  $J = 17.9$  Hz, 1H), 3.03 (dd,  $J = 17.0, 4.6$  Hz, 1H), 2.76 (dd,  $J = 17.0, 5.5$  Hz, 1H), 2.30 (m, 1H), 1.45 (s, 9H), 1.10 (m, 6H)

Less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (d,  $J = 8.7$  Hz, 1H), 8.32-8.26 (m, 2H), 8.17 (d,  $J = 8.7$  Hz, 1H), 7.91 (m, 2H), 7.80 (m, 1H), 7.66 (m, 1H), 7.28 (m, 4H), 7.02-6.87 (m, 6H), 5.01-4.77 (m, 4H), 4.38-4.30 (m, 2H), 3.50-3.38 (ABq,  $J = 17.9$  Hz, 2H), 3.06-3.02 (m, 1H), 2.84-2.80 (m, 1H), 2.34 (m, 1H), 1.44 (s, 9H), 1.14 (m, 6H)

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzyloxy)-pentanoic acid.

From more polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  9.01 (d,  $J = 9.2$  Hz, 1H), 8.87 (d,  $J = 8.3$  Hz, 1H), 8.55 (d,  $J = 8.3$  Hz, 1H),

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8.18-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.28-7.14 (m, 4H), 6.96-6.75 (m, 6H), 5.00-4.75 (m, 4H), 4.42 (d, J = 10.6 Hz, 1H), 4.22 (d, J = 10.6 Hz, 1H), 3.47-3.35 (ABq, J = 17.9 Hz, 2H), 2.82 (dd, J = 17.0, 6.4 Hz, 2.56 (m, 1H), 2.33 (m, 1H), 0.98 (m, 6H).

From less polar isomer:  $^1\text{H}$ -NMR (500 MHz, DMSO- $d_6$ )  $\delta$  9.06 (d, J = 9.2 Hz, 1H), 8.88 (d, J = 7.8 Hz, 1H), 8.57 (d, J = 8.7 Hz, 1H), 8.22-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.17 (m, 4H), 6.91-6.78 (m, 6H), 4.98-4.90 (ABq, J = 17.9 Hz, 2H), 4.77 (m, 2H), 4.35 (d, J = 10.6 Hz, 1H), 4.20 (d, J = 10.6 Hz, 1H), 3.47-3.35 (ABq, J = 18.3 Hz, 2H), 2.89 (dd, J = 17.0, 6.4 Hz, 2.61 (dd, J = 17.0, 6.4, 1H), 2.31 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H).

. (3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer:  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (d, J = 8.3 Hz), 7.94 (d, J = 8.3 Hz), 7.88 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 9.7 Hz, 1H), 7.61-7.44 (m, 4H), 7.35-7.18 (m, 8H), 6.23 (d, J = 8.7 Hz, 1H), 4.95 (m, 1H), 4.76 (m, 1H), 4.49-4.41 (ABq, J = 17.5 Hz, 2H), 3.49-3.41 (m, 2H), 3.22-3.12 (m, 2H), 2.92 (dd, J = 17.0, 4.2 Hz, 1H), 2.52 (dd, J = 17.0, 5.1 Hz, 1H), 2.13 (m, 1H), 1.37 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H).

Less polar isomer:  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (d, J = 8.3 Hz, 1H), 7.83 (m, 2H), 7.57-7.47 (m, 4H), 7.38-7.22 (m, 9H), 6.64 (d, J = 9.2 Hz, 1H), 5.00-4.87 (m, 3H), 4.72 (m, 1H), 3.60 (d, J = 17.9 Hz, 1H), 3.36 (d, J = 14.2 Hz, 1H), 3.20 (d, J = 14.2 Hz, 1H), 3.12 (d, J = 17.9

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Hz, 1H), 2.69 (dd, J = 17.0, 4.6 Hz, 1H), 2.28-2.18 (m, 2H), 1.38 (s, 9H), 1.06 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H).

. (3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester (more polar isomer)

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.72 (d, 1H), 7.62 (d, J = 15.6 Hz, 1H), 7.50 (m, 1H), 7.38-7.21 (m, 12H), 6.39 (d, J = 15.6 Hz, 1H), 5.90 (d, J = 9.2 Hz, 1H), 4.76 (m, 2H), 4.49-4.41 (ABq, J = 17.4 Hz, 2H), 3.42-3.38 (m, 2H), 3.17 (d, J = 14.2 Hz, 1H), 3.09 (d, J = 17.9 Hz, 1H), 2.91 (dd, J = 17.4, 4.6 Hz, 1H), 2.52 (dd, J = 17.4, 5.0 Hz, 1H), 2.04 (m, 1H), 1.41 (s, 9H), 0.90 (m, 6H).

Less polar isomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.61 (d, 1H), 7.52 (d, 1H), 7.41 (d, 1H), 7.28 (m, 12H), 6.64-6.41 (m, 2H), 5.09-4.99 (ABq, J = 17.4 Hz, 2H), 4.81 (m, 1H), 4.69 (m, 1H), 3.50 (d, J = 17.9 Hz, 1H), 3.34 (d, J = 14.2 Hz, 1H), 3.17 (d, J = 14.2 Hz, 1H), 3.04 (d, J = 17.9 Hz, 1H), 2.74 (dd, J = 17.0, 4.2 Hz, 1H), 2.22 (m, 2H), 1.39 (s, 9H), 0.97-0.88 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77 (d, J = 9.3 Hz, 1H), 7.38-7.23 (m, 13H), 4.80-4.63 (m, 2H), 4.56-4.46 (ABq, J = 17.1 Hz, 2H), 4.21-4.10 (m, 2H), 3.83 (m, 2H), 3.41-3.37 (m, 1H), 3.19 (d, J = 14.2 Hz, 1H), 2.90-2.83 (m, 2H), 2.53 (m, 1H), 1.76 (m, 1H), 1.41 (s,

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9H), 0.83 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).

Less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d, J = 9.2 Hz, 1H), 7.36-7.26 (m, 13H), 5.05-4.95 (m, 3H), 4.74 (m, 1H), 4.17 (m, 2H), 3.96 (m, 1H), 3.41-2.99 (m, 4H), 2.70 (m, 1H), 2.19 (m, 1H), 1.79 (m, 1H), 1.39 (s, 9H), 0.86 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.59 (d, J = 8.7 Hz, 1H), 8.31 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.78-7.72 (m, 2H), 7.62 (m, 1H), 7.33-7.27 (m, 3H), 5.20-5.05 (m, 3H), 4.92-4.89 (m, 2H), 3.47-3.34 (m, 2H), 2.95 (dd, J = 17.0, 4.6 Hz, 1H), 2.73 (dd, J = 17.0, 5.1 Hz, 1H), 2.28 (m, 1H), 1.45 (s, 9H), 1.07 (m, 6H).

Less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.58 (d, J = 9.2 Hz, 1H), 8.28-8.24 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75-7.59 (m, 3H), 7.31-7.25 (m, 3H), 5.12-4.89 (m, 5H), 3.46-3.41 (m, 2H), 2.92 (dd, J = 17.0, 5.1 Hz, 1H), 2.78 (dd, J = 17.0, 5.5 Hz, 1H), 2.30 (m, 1H), 1.44 (s, 9H), 1.10 (m, 6H)

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (d, J = 9.2 Hz,

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1H), 8.32 (d, J = 8.3 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.80-7.63 (m, 3H), 7.36-7.18 (m, 8H), 4.82 (m, 1H), 4.72 (m, 1H), 4.47-4.37 (ABq, J = 17.0 Hz, 2H), 3.47 (d, J = 17.9 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.19 (d, J = 14.2 Hz, 1H), 3.14 (d, J = 17.9 Hz, 1H), 2.94 (dd, J = 17.4, 4.1 Hz, 1H), 2.53 (dd, J = 17.0, 5.0 Hz, 1H), 2.18 (m, 1H), 1.45 (s, 9H), 0.98 (m, 6H).

Less polar isomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.52 (d, J = 9.2 Hz, 1H), 8.28-8.23 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.73 (m, 1H), 7.62-7.55 (m, 2H), 7.31-7.17 (m, 8H), 5.06-4.98 (ABq, J = 17.0 Hz, 2H), 4.84 (m, 1H), 4.69 (m, 1H), 5.54 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 14.2 Hz, 1H), 3.16 (d, J = 14.2 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 2.70 (dd, J = 17.0, 4.1 Hz, 1H), 2.21 (m, 1H), 2.11 (dd, J = 17.0, 5.1 Hz, 1H), 1.38 (s, 9H), 0.98 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester

More polar isomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.47 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.78 (m, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.29-7.17 (m, 4H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 4.81-4.72 (m, 2H), 4.47-4.28 (ABq, J = 17.9 Hz, 2H), 3.42 (d, J = 17.9 Hz, 1H), 3.34 (d, J = 14.2 Hz, 1H), 3.15 (d, J = 13.7 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 2.94 (dd, J = 17.4, 4.1 Hz, 1H), 2.64 (dd, J = 17.4, 5.5 Hz, 1H), 2.15 (m, 1H), 1.43 (s, 9H), 0.95 (m, 6H).

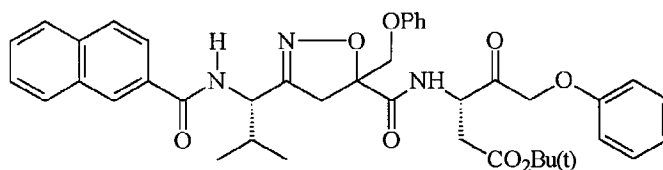
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Less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J = 9.2$  Hz, 1H), 8.24 (d,  $J = 8.3$  Hz, 1H), 8.18 (d,  $J = 8.3$  Hz, 1H), 8.10 (d,  $J = 8.2$  Hz, 1H), 7.85 (d,  $J = 7.7$  Hz, 1H), 7.74 (m, 1H), 7.62-7.56 (m, 2H), 7.29-7.16 (m, 5H), 6.88 (t,  $J = 7.4$  Hz, 1H), 6.78 (d,  $J = 7.8$  Hz, 2H), 4.81-4.66 (m, 4H), 3.46 (d,  $J = 17.9$  Hz, 1H), 3.29 (d,  $J = 13.8$  Hz, 1H), 3.15 (d,  $J = 13.8$  Hz, 1H), 3.07 (d,  $J = 17.9$  Hz, 1H), 2.76 (dd,  $J = 17.0$ , 4.1 Hz, 1H), 2.21-2.09 (m, 2H), 1.37 (s, 9H), 0.93 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydroisoxazole-5-carbonylamino}-4-keto-pentanoic acid t-butyl ester

Diastereomeric mixture:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (m, 1H), 7.96-7.50 (m, 7H), 6.85-6.73 (m, 1H), 5.10-4.97 (m, 2H), 4.66 (m, 1H), 3.40 (m, 2H), 2.94-2.60 (m, 2H), 2.32-2.14 (m, 1H), 2.22 & 2.10 (two s, 3H), 1.43 & 1.42 (two s, 9H), 1.10-0.95 (m, 6H).

Example 23: Synthesis of (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester



The title compound was prepared with conventional EDC coupling of 3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (1.00g, 2.24 mmol) and (3S)-3-amino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester (630 mg, 1.0 eq), EDC (558 mg, 1.3 eq), HOBT (394 mg, 1.3 eq) and triethylamine

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(0.94 mL, 3.0 eq) in DMF (5 mL). Usual workup followed by flash chromatography gave 1.44g of coupled product. The coupled product and Dess-Martin reagent (2.15g, 2.5 mol eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (25mL) under N<sub>2</sub> at room temperature was stirred for 1h, then quenched with isopropyl alcohol(3 mL). Usual extractive workup followed by flash chromatography (36% ethyl acetate-hexane) gave 1.27g of the title compound as diastereomeric mixture. Preparative HPLC (36% ethyl acetate-hexanes, 10 mL/min, 278 nm UV detection) afforded less polar (352 mg) and more polar (536 mg) diastereomers.

Less polar diastereomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.29 (1H, s), 7.93-7.81 (5H, m), 7.58-7.51 (2H, m), 7.28-7.21 (4H, m), 6.99-6.76 (7H, m), 5.00-4.98 (2H, m), 4.79-4.66 (2H, ABq, J = 16.6 Hz), 4.35-4.29 (2H, ABq, J = 10.3 Hz), 3.40 (2H, s), 3.02-2.98 (1H, dd, J = 16.6, 4.9 Hz), 2.84-2.79 (1H, dd, J = 16.6, 4.7 Hz), 2.30 (1H, m), 1.41 (9H, s), 1.12-1.07 (6H, two d, J = 6.8 Hz).

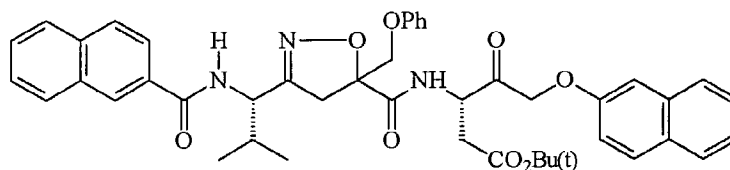
More polar diastereomer: <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 8.29 (1H, s), 7.99-7.82 (5H, m), 7.59-7.53 (2H, m), 7.26-7.18 (4H, m), 6.97-6.83 (6H, m), 6.68 (1H, d, J = 8.3 Hz), 5.01-4.95 (3H, m), 4.83 (1H, d, J = 17.1 Hz), 4.42 (1H, d, J = 9.8 Hz), 4.23 (1H, d, J = 9.8 Hz), 3.49-3.32 (2H, ABq, J = 18.1 Hz), 3.06-3.02 (1H, dd, J = 17.1, 4.4 Hz), 2.76-2.72 (1H, dd, J = 17.1, 5.4 Hz), 2.24 (1H, m), 1.45 (9H, s), 1.10-1.02 (6H, two d, J = 6.8 Hz).

The following compounds were prepared similarly:

• (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carboxylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxyl-amino}-4-keto-5-(2-naphthoxy)-pen

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tanoic acid-t-butyl ester



Less polar diastereomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27(1H, s), 7.89 (8H, m), 7.56-7.26 (6H, m), 7.23-6.87 (5H, m), 6.74 (1H, d,  $J = 9.3$  Hz), 5.04-4.95 (2H, m), 4.92-4.80 (2H, ABq,  $J = 16.6$  Hz), 4.37-4.30 (2H, ABq,  $J = 23.4, 10.3$  Hz), 3.43-3.38 (2H, ABq,  $J = 22.5, 17.8$  Hz), 3.05-3.00 (1H, dd,  $J = 16.6, 4.9$  Hz), 2.86-2.82 (1H, dd,  $J = 16.6, 4.9$  Hz), 2.25 (1H, m), 1.42 (9H, s), 1.09-1.05 (6H, two d,  $J = 6.8, 6.7$  Hz).

More polar diastereomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (1H, s), 8.02-7.55 (10H, m), 7.41-7.05 (6H, m), 6.89-6.66 (4H, m), 5.10-4.94 (4H, m), 4.41 (1H, d,  $J = 9.8$  Hz), 4.23 (1H, d,  $J = 10.3$  Hz), 3.50-3.34 (2H, ABq,  $J = 17.6$  Hz), 3.09-3.05 (1H, dd,  $J = 17.1, 4.4$  Hz), 2.79-2.74 (1H, dd,  $J = 17.1, 5.4$  Hz), 2.25 (1H, m), 1.45 (9H, s), 1.10-1.02 (6H, two d,  $J = 6.8$  Hz).

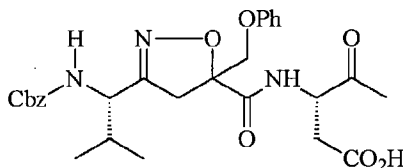
. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester

More polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (d,  $J = 9.2$  Hz, 1H), 8.32-8.25 (m, 2H), 8.13 (d,  $J = 8.8$  Hz, 1H), 7.88 (d,  $J = 7.8$  Hz, 1H), 7.79-7.62 (m, 3H), 7.27 (m, 2H), 6.97 (m, 1H), 6.88 (m, 2H), 5.04-4.72 (m, 5H), 3.48-3.34 (m, 2H), 3.00 (dd,  $J = 17.0, 4.6$  Hz, 1H), 2.77 (dd,  $J = 17.0, 5.5$  Hz, 1H), 2.27 (m, 1H), 1.45 (s, 9H), 1.06 (m, 6H).

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Less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.58 (d,  $J = 9.2$  Hz, 1H), 8.27 (d,  $J = 8.2$  Hz, 1H), 8.21 (d,  $J = 8.3$  Hz, 1H), 8.13 (d,  $J = 8.3$  Hz, 1H), 7.86 (d,  $J = 8.3$  Hz, 1H), 7.78-7.59 (m, 3H), 7.22 (m, 2H), 6.92 (m, 1H), 6.82 (m, 2H), 5.04-4.88 (m, 3H), 4.82-4.69 (ABq,  $J = 17.0$  Hz, 2H), 3.45-3.33 (m, 2H), 2.99 (dd,  $J = 16.5, 4.6$  Hz, 1H), 2.78 (dd,  $J = 16.5, 5.1$  Hz, 1H), 2.26 (m, 1H), 1.42 (s, 9H), 1.06 (m, 6H)

Example 24: Synthesis of (3S)-3-{3-[(1S)-1-benzyloxycarbonylamino-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid



A solution of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid t-butyl ester (less polar diastereomer) (44mg) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at  $0^\circ\text{C}$  was treated with TFA (1 mL). The reaction was stirred for 2h while slowly warming to room temperature. Concentration gave the title compound (compound 2, quantitative)

$^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.35-6.90 (10H, m), 5.11 (2H, s), 4.53 (1H, m), 4.47 (1H, m), 4.23 (2H, dd), 2.86 (1H, dd), 2.54 (1H, dd), 2.24 (3H, s), 2.00 (1H, m), 1.00 and 0.97 (6H, two d); MS  $[\text{M}+\text{Na}]^+$  562

The following compound was prepared similarly from more polar isomer:

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. (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid (compound 3).

$^1\text{H}$  NMR (500 MHz, )  $\delta$  8.76 (1H,d, J = 7.8 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.36-6.87 (10H, m), 5.06 (2H, m), 4.50 (1H, m), 4.32 (1H, m), 4.16 (2H, m), 3.21 (2H, app s), 2.79 (1H, m), 2.06 (3H, s), 1.89 (1H, m), 0.91 (3H, d, J = 6.3 Hz), 0.80 (3H, d, J = 6.3 Hz).

Following final compounds were obtained by similar TFA deprotection of corresponding t-butyl ester.

. (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 1, diastereomeric mixture)

$^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.49 (1H, m), 7.72 (1H, m), 7.35 (5H, m), 5.03 (3H, m), 4.40 (1H, m), 4.15 (1H, m), 3.24 (2H, m), 2.54 (2H, m), 2.04 and 1.95 (3H, wo s), 1.88 (1H, m), 0.90-0.81 (6H, m): MS  $[\text{M}+\text{Na}]^+$  456

. (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 6, diastereomeric mixture)

$^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.58 (1H, br s), 7.75 (1H, m), 7.61-7.30 (8H, m), 5.30-5.00 (5H, m), 4.70 (1H, m), 4.16 (1H, m), 2.66 (2H, m), 1.90 (1H, m), 0.95-0.79 (6H, m): MS  $[\text{M}+\text{Na}]^+$  644

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. (3S)-3-{3-[(1S)-1-(naphthalene-1-carboxylamino)-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-phenoxy-pentanoic acid (compound 7, diastereomeric mixture)

$^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.92-8.55 (2H, m), 8.15-7.98 (3H, m), 7.63-7.55 (4H, m), 7.25-7.15 (4H, m), 6.95-6.74 (6H, m), 5.20-4.15 (6H, m), 2.80-2.55 (2H, m), 2.05 (1H, m), 1.05-0.89 (6H, m): MS  $[\text{M}+\text{Na}]^+$  674.

. (3S)-3-{3-[(1S)-1-(naphthalene-2-carboxylamino)-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-phenoxy-pentanoic acid (compound 8)

From less polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.93 (1H, d,  $J = 7.8$  Hz), 8.79 (1H, d,  $J = 8.3$  Hz), 8.48 (1H, s), 8.05-7.94 (4H, m), 7.64-7.58 (2H, m), 7.30-7.17 (4H, m), 6.94-6.83 (6H, m), 4.96 (2H, app s), 4.78 (1H, m), 4.73 (1H, m), 4.36 (1H, d,  $J = 10.2$  Hz), 4.22 (1H, d,  $J = 10.2$  Hz), 3.37 (2H, app s), 2.91 (1H, dd,  $J = 16.6, 6.4$  Hz), 2.62 (1H, dd,  $J = 16.6, 5.9$  Hz), 2.12 (1H, m), 1.00 (3H, d,  $J = 6.3$  Hz), 0.87 (3H, d,  $J = 6.3$  Hz): MS  $[\text{M}+\text{Na}]^+$  674

From more polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.88 (1H, d,  $J = 8.3$  Hz), 8.79 (1H, d,  $J = 8.8$  Hz), 8.43 (1H, s), 8.00-7.80 (4H, m), 7.61 (2H, m), 7.23-7.17 (4H, m), 6.93-6.77 (6H, m), 4.99 (1H, d,  $J = 17.6$  Hz), 4.86 (1H, d,  $J = 18.1$  Hz), 4.79 (1H, m), 4.72 (1H, m), 4.43 (1H, d,  $J = 10.7$  Hz), 4.20 (1H, d,  $J = 10.2$  Hz), 2.81 (1H, dd), 2.56 (1H, dd), 2.17 (1H, m), 1.01 (3H, d,  $J = 6.3$  Hz), 0.99 (3H, d,  $J = 6.3$  Hz): MS  $[\text{M}+\text{Na}]^+$  674

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. (3S)-3-{3-[(1S)-1-(naphthalene-1-carboxylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 9)

From less polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  9.08 (1H, d,  $J = 7.8$  Hz), 8.87 (1H, d,  $J = 8.8$  Hz), 8.55 (1H, s), 8.10-8.01 (4H, m), 7.68-7.58 (5H, m), 7.26 (2H, t,  $J = 7.8$  Hz), 6.98-6.92 (3H, m), 5.27 (2H, ABq,  $J = 16.6$  Hz), 4.82-4.78 (2H, m), 4.43 (1H, d,  $J = 10.7$  Hz), 4.29 (1H, d,  $J = 10.3$  Hz), 3.44 (2H, ABq,  $J = 18.1$  Hz), 3.01 (1H, dd,  $J = 17.1, 6.4$  Hz), 2.67 (1H, dd,  $J = 17.1, 6.3$  Hz), 2.21 (1H, m), 1.07 (3H, d,  $J = 6.2$  Hz), 0.97 (3H, d,  $J = 6.2$  Hz): MS  $[\text{M}+\text{Na}]^+$  770

From more polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.97 (1H, d,  $J = 7.8$  Hz), 8.85 (1H, d,  $J = 8.3$  Hz), 8.50 (1H, s), 8.09-7.96 (4H, m), 7.67-7.60 (5H, m), 7.32 (2H, t,  $J = 6.3$  Hz), 7.00 (3H, m), 5.38 (1H, d,  $J = 17.1$  Hz), 5.13 (1H, d,  $J = 17.1$  Hz), 4.92 (1H, d,  $J = 6.3$  Hz), 4.79 (1H, t,  $J = 7.8$  Hz), 4.55 (1H, d,  $J = 9.7$  Hz), 4.28 (1H, d,  $J = 8.7$  Hz), 3.48 (1H, d,  $J = 18.1$  Hz), 3.38 (1H, d,  $J = 18.1$  Hz), 2.87 (1H, dd,  $J = 17.1, 4.9$  Hz), 2.60 (1H, dd,  $J = 17.1, 4.9$  Hz), 2.25 (1H, m), 1.07 (6H, m): MS  $[\text{M}+\text{Na}]^+$  770

. (3S)-3-{3-[(1S)-1-(naphthalene-2-carboxylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 10, diastereomeric)

$^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.72-8.55 (2H, m), 8.38 (1H, s), 8.04-7.85 (4H, m), 7.62 (2H, m), 7.25-7.12 (7H, m), 6.91-6.70 (3H, m), 4.79-4.51 (4H, m), 3.40-3.05 (4H, m), 2.73-2.23 (2H, m), 2.01 (1H, m), 0.94-0.70 (6H, m): MS  $[\text{M}+\text{Na}]^+$  658

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. (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 11)

From less polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.68 (1H, d,  $J = 8.8$  Hz), 8.59 (1H, d,  $J = 8.3$  Hz), 8.40 (1H, s), 8.05-7.87 (4H, m), 7.63-7.54 (5H, m), 7.21-7.13 (5H, m), 5.98 (2H, ABq,  $J = 17.1$  Hz), 4.74 (1H, m), 4.64 (1H, m), 3.25-3.10 (4H, m), 2.62 (1H, dd,  $J = 17.1, 6.3$  Hz), 2.37 (1H, dd,  $J = 16.6, 5.4$  Hz), 2.06 (1H, m), 0.93 (3H, d,  $J = 6.8$  Hz), 0.83 (3H, d,  $J = 6.2$  Hz): MS  $[\text{M}+\text{Na}]^+$  754

From more polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.72 (1H, d,  $J = 8.3$  Hz), 8.59 (1H, d,  $J = 8.8$  Hz), 8.41 (1H, s), 8.01-7.87 (4H, m), 7.62-7.53 (5H, m), 7.29-7.21 (5H, m), 4.70-4.55 (4H, m), 3.44-3.10 (4H, m), 2.72-2.67 (1H, dd,  $J = 16.6, 7.3$  Hz), 2.38-2.34 (1H, dd,  $J = 16.6, 7.3$  Hz), 2.05 (1H, m), 0.97 (3H, d,  $J = 6.3$  Hz), 0.79 (3H, d,  $J = 6.3$  Hz); MS  $[\text{M}+\text{Na}]^+$  754.

. (3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 13, diastereomeric mixture)

$^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  9.06 (1H, m), 8.82 (1H, br), 8.57 (1H, m), 8.16-7.74 (9H, m), 7.26-7.12 (4H, m), 6.89-6.69 (6H, m), 5.10-4.70 (4H, m), 4.48-4.20 (2H, m), 2.87-2.53 (2H, m), 2.32 (1H, m), 0.98-0.85 (6H, m): MS  $[\text{M}+\text{Na}]^+$  675,  $[\text{M}+\text{H}]^+$  653.

. (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy

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ymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid  
(compound 15)

From less polar t-butyl ester:  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.96 (1H, d,  $J = 7.8$  Hz), 8.77 (1H, d,  $J = 8.3$  Hz), 8.47 (1H, s), 8.03-7.57 (9H, m), 7.44 (1H, t,  $J = 6.8$  Hz), 7.34 (1H, t,  $J = 7.8$  Hz), 7.17-7.13 (4H, m), 6.88-6.82 (3H, m), 5.09 (2H, ABq), 4.84 (1H, m), 4.72 (1H, m), 4.38 (1H, d,  $J = 10.2$  Hz), 4.23 (1H, d,  $J = 10.7$  Hz), 2.94 (1H, dd,  $J = 17.1, 6.8$  Hz), 2.65 (1H, dd,  $J = 16.6, 5.9$  Hz), 2.12 (1H, m), 0.97 (3H, d,  $J = 6.3$  Hz), 0.85 (3H, d,  $J = 6.3$  Hz): MS  $[\text{M}+\text{Na}]^+$  724

From more polar t-butyl ester:  $^1\text{H}$  NMR (50°C, 300 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.72 (1H, d), 8.63 (1H, d), 8.41 (1H, s), 7.94-6.72 (19H, m), 5.03 (2H, ABq), 4.88 (1H, m), 4.74 (1H, m), 4.42 (1H, d), 4.19 (1H, m), 3.38 (2H, ABq), 2.88 (1H, dd), 2.65 (1H, dd), 2.19 (1H, m), 1.02 (6H, two d): MS  $[\text{M}+\text{Na}]^+$  724

$^{13}\text{C}$  NMR (50°C, 300 MHz, DMSO- $\text{d}_6$ )  $\delta$  202.1, 171.6, 170.7, 166.6, 159.3, 158.0, 155.6, 134.1, 133.9, 132.0, 131.6, 129.3, 129.1, 128.7, 127.7, 127.5, 127.3, 126.5, 126.2, 124.2, 123.6, 121.1, 118.1, 114.5, 107.4, 87.5, 70.2, 52.9, 34.4, 29.6, 19.4, 18.9.

More polar diastereomer's methyl ester:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (1H, s), 8.02-6.68 (20H, m), 5.09-4.95 (2H, ABq,  $J = 16.6$  Hz), 5.10 (1H, m), 5.01 (1H, m), 4.34 (2H, ABq,  $J = 10.3$  Hz), 3.70 (3H, s), 3.50-3.33 (2H, ABq,  $J = 17.6$  Hz), 3.13 (1H, dd,  $J = 17.1, 4.9$  Hz), 2.90 (1H, dd,  $J = 17.1, 5.9$  Hz), 2.23 (1H, m), 1.08 and 1.02 (6H, two d,  $J = 6.8$  Hz).

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. (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid (compound 16, diastereomeric mixture)

<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 9.02-8.18(3H, m), 8.05-6.80 (18H, m), 5.15-4.15 (6H, m), 2.90-2.55 (2H, m), 2.14 (1H, m), 1.05-0.82 (6H, m).

. (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid (compound 19, diastereomeric mixture)

<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.95-8.46 (3H, m), 8.09-7.07 (13H, m), 5.21-4.75 (5H, m), 2.95-2.64 (2H, m), 2.19 (1H, m): MS [M+H]<sup>+</sup> 596

. (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 20, diastereomeric mixture)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.76-8.69 (m, 2H), 8.45 (m, 1H), 8.04-7.90 (m, 5H), 7.61 (m, 2H), 7.31-7.19 (m, 2H), 6.97-6.81 (m, 3H), 5.09-4.68 (m, 5H), ~3.3 (m, 2H), 2.82 (m, 1H), 2.64 (m, 1H), 2.15 ((m, 1H), 1.00-0.84 (m, 6H): MS [M+Na] = 568

. (3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 22, diastereomeric mixture)

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$^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.48 (br s, 1H), 8.00 (m, 1H), 7.61-7.54 (m, 3H), 7.30-7.15 (m, 11H), 4.93-4.32 (m, 4H), 3.34-2.90 (m, 4H), 2.78 (m, 1H), 1.78 (m, 1H), 0.90-0.60 (m, 6H): MS  $[\text{M}+\text{Na}] = 732$

. (3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 23)

From more polar t-butyl ester:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.80 (d,  $J = 8.3$  Hz, 1H), 8.63 (d,  $J = 7.8$  Hz, 1H), 8.02 (m, 3H), 7.64-7.20 (m, 12H), 4.81-4.55 (m, 4H), 3.39 (m, 2H), 3.12 (m, 2H), 2.73 (m, 1H), 2.43 (m, 1H), 1.98 (m, 1H), 0.99 (d,  $J = 4.6$  Hz, 3H), 0.79 (d,  $J = 4.5$  Hz, 3H): MS  $[\text{M}+\text{Na}] = 754$

From less polar t-butyl ester:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.77 (d,  $J = 8.7$  Hz, 1H), 8.62 (d,  $J = 8.3$  Hz, 1H), 8.08-7.97 (m, 4H), 7.61-7.21 (m, 12H), 5.00 (m, 2H), 4.77-4.67 (m, 2H), 3.39-3.27 (m, 2H), 3.15-3.11 (m, 2H), 2.64 (m, 1H), 2.40 (m, 1H), 1.99 (m, 1H), 0.96 (d,  $J = 6.4$  Hz, 3H), 0.85 (d,  $J = 6.9$  Hz, 3H).

. (3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 28)

From more polar t-butyl ester:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.55 (d,  $J = 8.7$  Hz, 1H), 8.28 (d,  $J = 8.7$  Hz, 1H), 7.60-7.19 (m, 14H), 6.70 (d,  $J = 15.6$  Hz, 1H), 4.71-4.49 (m, 4H), ~3.3 (m, 2H), 3.08 (m, 2H), 2.71 (m, 1H), 2.40 (m, 1H), 1.90 (m, 1H), 0.86 (d,  $J = 6.4$  Hz, 3H), 0.74 (d,  $J = 6.4$  Hz, 3H): MS  $[\text{M}+\text{H}] = 708$

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From less polar t-butyl ester:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.53 (d,  $J = 8.3$  Hz, 1H), 8.28 (d,  $J = 8.7$  Hz, 1H), 7.61-7.16 (m, 14H), 6.69 (d,  $J = 16.9$  Hz, 1H), 4.99-4.92 (ABq,  $J = 17.4$  Hz, 2H), 4.72 (m, 1H), 4.53 (m, 1H), 3.36 (d,  $J = 17.9$  Hz, 1H), 3.23 (d,  $J = 13.8$  Hz, 1H), 3.10-3.04 (m, 2H), 2.61 (dd,  $J = 17.0, 6.4$  Hz, 1H), 2.37 (dd,  $J = 17.0, 6.0$  Hz, 1H), 1.90 (m, 1H), 0.79 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 29, diastereomeric)

$^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.75 and 7.69 (m, 1H), 7.61-7.13 (m, 13H), 5.00 and 4.70 (m, 1H), 4.64 (m, 2H), 4.22-3.78 (m, 4H), 1.79 (m, 1H), 0.90 (m, 6H):MS  $[\text{M}+\text{H}] = 732$ .

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 30)

From more polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.94 (d,  $J = 9.7$  Hz, 1H), 8.75 (d,  $J = 7.8$  Hz, 1H), 8.55 (d,  $J = 8.8$  Hz, 1H), 8.18-8.05 (m, 3H), 7.85 (m, 1H), 7.55 (m, 3H), 5.22-5.06 (m, 3H), 4.83-4.70 (m, 2H), 3.35 (m, 2H), 2.80 (m, 1H), 2.61 (m, 1H), 2.31 (m, 1H), 0.95 (m, 6H):MS  $[\text{M}+\text{H}] = 643$

From less polar isomer:  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  9.07 (d,  $J = 9.2$  Hz, 1H), 8.76 (d,  $J = 8.3$  Hz, 1H), 8.56 (d,  $J = 8.7$  Hz, 1H), 8.20-8.07 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.62-7.54 (m, 3H),

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5.21-5.06 (m, 3H), 4.84-4.70 (m, 2H), 3.44-3.27 (m, 2H), 2.85 (dd, J = 17.0, 6.0, 1H), 2.66 (dd, J = 17.0, 6.9 Hz, 1H), 2.29 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.4 Hz, 6H)

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 31)

From more polar isomer:  $^1\text{H-NMR}$  (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.95 (d, 1H), 8.72 (d, 1H), 8.55 (d, 1H), 8.20-8.05 (m, 3H), 7.86 (m, 1H), 7.72 (m, 1H), 7.24-6.74 (m, 5H), 5.11-4.70 (m, 5H), 3.34 (m, 2H), 2.80 (m, 1H), 2.62 (m, 1H), 2.30 (m, 1H), 0.95 (m, 6H):MS  $[\text{M}+\text{H}] = 547$

From less polar isomer:  $^1\text{H-NMR}$  (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  9.03 (d, 1H), 8.74 (d, 1H), 8.56 (d, 1H), 8.20-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.23 (m, 2H), 6.88 (m, 3H), 5.09-4.71 (m, 5H), 3.34 (m, 2H), 2.85 (m, 1H), 2.65 (m, 1H), 2.27 (m, 1H), 0.96-0.87 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 32)

From more polar isomer:  $^1\text{H-NMR}$  (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.91 (d, J = 9.2 Hz, 1H), 8.59-8.52 (m, 2H), 8.17-8.06 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.58-7.53 (m, 5H), 4.69-4.51 (m, 4H), 3.40 (m, 2H), 3.16 (m, 1H), 2.69 (m, 1H), 2.37 (m, 1H), 2.19 (m, 1H), 0.91-0.80 (m, 6H): MS  $[\text{M}+\text{H}] = 733$

From less polar isomer:  $^1\text{H-NMR}$  (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.92 (d, J = 9.2 Hz, 1H), 8.56(m, 2H), 8.19-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H),

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7.60-7.54 (m, 3H), 7.22-7.07 (m, 5H), 5.01-4.93 (ABq, J = 16.5 Hz, 2H), 4.75-4.62 (m, 2H), 3.46 (d, J = 18.4 Hz, 1H), 3.23-3.07 (m, 3H), 2.62 (dd, J = 17.0, 6.9 Hz, 1H), 2.37 (dd, J = 17.0, 6.0 Hz, 1H), 2.21 (m, 1H), 0.86-0.83 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 33)

From more polar isomer:  $^1\text{H-NMR}$  (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.91 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.07 (m, 2H), 7.86 (m, 1H), 7.72 (m, 1H), 7.26-7.09 (m, 7H), 6.86 (m, 1H), 6.69 (d, J = 8.3 Hz, 2H), 4.71-4.63 (m, 2H), 4.54-4.46 (ABq, J = 17.9 Hz, 2H), 3.42 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.15 (d, J = 18.4 Hz, 1H), 3.09 (d, J = 14.3 Hz, 1H), 2.72 (dd, J = 17.0, 6.9 Hz, 1H), 2.36 (dd, J = 17.0, 6.0 Hz, 1H), 2.15 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H): MS [M+H] = 637

From less polar isomer:  $^1\text{H-NMR}$  (500 MHz, DMSO- $\text{d}_6$ )  $\delta$  8.88 (d, J = 9.6 Hz, 1H), 8.54 (m, 2H), 8.18-8.06 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.28-6.78 (m, 10H), 4.78-4.63 (m, 4H), 3.45 (d, J = 18.3 Hz, 1H), 3.26-3.06 (m, 3H), 2.66-2.62 (dd, J = 17.0, 6.9 Hz, 1H), 2.44-2.39 (dd, J = 17.0, 5.5 Hz, 1H), 2.17 (m, 1H), 0.80 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-imidazolymethyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 34, diastereomeric mixture)

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ 9.09-6.60 (m, 16H), 4.92-4.62 (m, 6H), 3.50 (m, 2H), 2.85-2.20 (m, 3H), 0.93 (m, 6H): MS [M+H] = 627

. (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydroisoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 35, diastereomeric mixture)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.77 (m, 1H), 8.45 (m, 2H), 8.07-7.89 (m, 4H), 7.61 (m, 2H), 5.06 (m, 1H), 4.72 (m, 1H), 4.46 & 4.38 (two m, 1H), ~3.3 (m, isoxazoline CH<sub>2</sub>), 2.62 (m, 1H), ~2.49 (m, 1H), 2.13 (m, 1H), 2.09 & 2.05 (two s, 3H), 1.01-0.84 (m, 6H).

. (3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydroisoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 36, diastereomeric mixture)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.56-8.52 (m, 1H), 8.15 (m, 1H), 7.27 (m, 2H), 6.97-6.82 (m, 3H), 4.96-4.83 (m, 2H), 4.77 (m, 1H), 4.58 (m, 1H), 3.58-2.22 (m, 10H), 2.0-1.74 (m, 2H), 1.47 & 1.45 (two s, 3H): MS [M+Na] = 558.

. (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydroisoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 37, diastereomeric mixture)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.62-8.52 (m, 1H), 8.06 (m, 1H), 7.27 (m, 2H), 6.96-6.81 (m, 3H), 4.94-4.72 (m, 3H), 4.43-4.32 (m, 1H), 3.38-3.22 (m, 1H), 2.94-2.78 (m, 2H), 2.70-2.22 (m, 5H), 1.95-1.77 (m, 1H), 1.48 & 1.46 (two s, 3H), 0.86-0.70 (m, 6H): MS [M+Na] = 528.

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. (3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid (compound 38, diastereomeric)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.75 (m, 1H), 8.47 and 8.29 (m, 1H), 8.03-7.23 (m, 12H), 4.65 (m, 2H), 3.11-2.99 (m, 2H), 2.26-2.18 (m, 4H), 1.97 (m, 1H), 1.64-0.79 (m, 12H); MS [M+H] = 627.

### **Industrial Applicability**

#### **Experiment 1: Screening on caspases enzyme inhibiting activity**

In the present experiment, recombinant caspases were purified from a transformed bacterium after human caspase genes were cloned into an expression vector pET, and then used in the experiment (Thornberry, N.A. et al. *Nature*, 1992, 356, 768. Thornberry, N.A. *Methods in Enzymology*, 1994, 615.).

Enzymatic activity was measured by a known procedure (Walker N.P.C. et al., *Cell* 1994, 78, 343). Briefly, 10 ng of recombinant protein was mixed with 50 mM Tris[pH 7.0], 1mM DTT, 0.5 mM EDTA, 10% Glycerol buffer containing 1~100 uM of enzyme substrate, Ac-YVAD-AMC or Ac-DEVD-AMC and then the changes by isolated AMC at 37°C were recorded. The inhibitory activity for caspases was calculated from the early enzyme reaction rate by measuring the changes with fluorescence excited at 380 nM and emitted at 460 nm (Range; K<sub>i</sub><100nM).

#### **Experiment 2) Screening for intracellular inhibitory efficacy for caspases**

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Inhibitory activity for Caspase-1 was determined by screening the effects of compounds on the IL-1 $\beta$  production in the periphery lymphocytes stimulated with LPS. Briefly, 500,000 cells/ml of human peripheral lymphocytes was treated with various concentration of test compounds for 2 hours and then with 10 ng/ml of LPS. After incubating the cells for 12 hours, the supernatant samples from the media were analysed by immunoantibody analysis (Amersham) in which 100 ng/well of human IL-1 $\beta$  antibody is coated (Range: CIC<sub>50</sub> : 0.1 ~ 10  $\mu$  M).

Meanwhile, the efficacy of the compounds on apoptosis was quantified by MTT assay in which cell death and survival ratio depending on the concentration of compounds were analyzed in Jurkat T cell treated with Anti-FAS antibody CH11 which induces cell death (Effective range; 1.0 ~ 10  $\mu$  M).

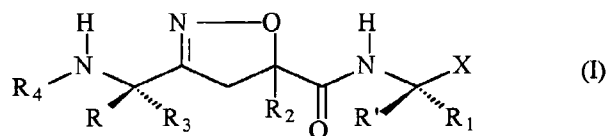
**Table 1**

compound	Ki for caspase-1	CIC <sub>50</sub> (IL-1 $\beta$ production)	ED <sub>50</sub> FAS Induced cell death
11	< 100 nM	0.1-10 $\mu$ M	1-10 $\mu$ M
13	"	"	"
18	"	"	"
21	"	"	"
22	"	"	"
23	"	"	"
28	"	"	"
30	"	"	"
32	"	"	"
33	"	"	"
36	"	"	"
37	"	"	"

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Claims

1. An isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, the esters and the stereochemically isomeric forms thereof



in which,

R and R' each independently represents simple alkyl chain (-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar) or hydrogen;

R<sub>1</sub> represents -SAC, -SCAC, -Ar, or -SAC-Ar and/or contains side chain residues of natural amino acids, or represent -CH<sub>2</sub>COOH;

R<sub>3</sub> represents -SAC, -SCAC, -Ar, or -SAC-Ar and/or contains side chain residues of natural amino acids, or represent -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>COOH, -(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>C(=O)NH<sub>2</sub> or -(CH<sub>2</sub>)<sub>2</sub>C(=O)NH<sub>2</sub>;

R<sub>2</sub> represents -H, -SAC, -SCAC, -Ar, or -SAC-Ar and contains side chain residues of natural amino acids or -(CH<sub>2</sub>)<sub>n</sub>(O)<sub>m</sub>R<sub>5</sub> (in which R<sub>5</sub> = -SAC, -SCAC, -Ar, -SAC-Ar; and n=0, 1, 2; m=0, 1), or -(CH<sub>2</sub>)<sub>n</sub>OC(=O)R<sub>6</sub> (in which R<sub>6</sub> = -SAC, -SCAC, -Ar, or -SAC-Ar; and n=1, 2) or represents (CH<sub>2</sub>)<sub>n</sub>(O)<sub>m</sub>Ar' (in which n=0, 1, 2; m=0,1; Ar'=substituted phenyl or imidazole), methyl or hydrogen;

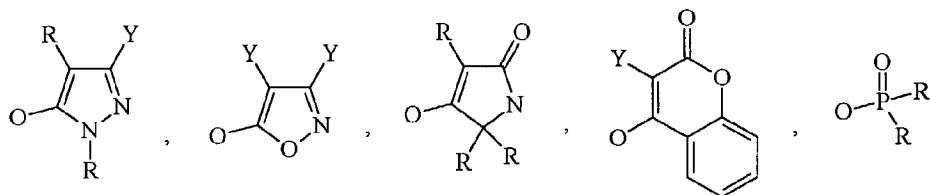
R<sub>4</sub> represents an organic acid acyl group of all the natural amino acids or represents -C(=O)R<sub>7</sub> (in which R<sub>7</sub> = -SAC, -SCAC, -Ar, or -SAC-Ar),

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-C(=O)OR<sub>8</sub> (in which R<sub>8</sub> = -SAC, -SCAC, -Ar, or -SAC-Ar),  
 -C(=O)NR<sub>9</sub>R<sub>10</sub> (in which R<sub>9</sub>, R<sub>10</sub> = -H, -SAC, -SCAC, -Ar, or -SAC-Ar),  
 -SOR<sub>11</sub> (in which R<sub>11</sub> = -SAC, -SCAC, -Ar, or -SAC-Ar), or -SO<sub>2</sub>R<sub>12</sub> (in  
 which R<sub>12</sub> = -SAC, -SCAC, -Ar, or -SAC-Ar);

In cases where R<sub>1</sub> and the adjacent R', and/or R<sub>3</sub> and the adjacent R are  
 connected to each other to form a cyclic compound, R<sub>1</sub>-R' or R<sub>3</sub>-R  
 together represents (CH<sub>2</sub>)<sub>n</sub>, (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>, or (CH<sub>2</sub>)<sub>n</sub>-NR<sub>13</sub>-(CH<sub>2</sub>)<sub>m</sub> [in  
 which n+m < 9, R<sub>13</sub> = -SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC,  
 -C(=O)-SCAC, -C(=O)-Ar, or -C(=O)-SAC-Ar];

X represents -CN, -CHO, -C(=O)R<sub>14</sub> [in which R<sub>14</sub> = -SAC, -SCAC, -Ar,  
 or -SAC-Ar], -C(=O)OR<sub>15</sub> [in which R<sub>15</sub> = -SAC, -SCAC, -Ar, or  
 -SAC-Ar], -CONR<sub>16</sub>R<sub>17</sub> [in which R<sub>16</sub> and R<sub>17</sub> each represents -H, -SAC,  
 -SCAC, -Ar, or -SAC-Ar], -C(=O)CH<sub>2</sub>OR<sub>18</sub> [in which R<sub>18</sub> represents -SAC,  
 -SCAC, -Ar, or -SAC-Ar], or -C(=O)CH<sub>2</sub>OC(=O)R<sub>19</sub> [in which R<sub>19</sub> =  
 -SAC, -SCAC, -Ar, or -SAC-Ar]. The invention further encompasses a  
 case where if X represents -COCH<sub>2</sub>-W, W represents -N<sub>2</sub>, -F, -Cl, -Br, -I,  
 -NR<sub>20</sub>R<sub>21</sub> or -SR<sub>22</sub> [in which wherein R<sub>20</sub>, R<sub>21</sub> and R<sub>22</sub> each independently  
 represents -SAC, -SCAC, -Ar, or -SAC-Ar or a case where R<sub>20</sub> and R<sub>21</sub>  
 are connected to form a cyclic compounds]; W also represents



in which Y represents -OH, OR<sub>23</sub> (in which R<sub>23</sub> = -SAC, or -SCAC),  
 -C(=O)R<sub>24</sub> (in which R<sub>24</sub> = -H, -SAC, or -SCAC), -F, -Cl, -Br, -I, -CN,  
 -NC, -N<sub>3</sub>, -CO<sub>2</sub>H, CF<sub>3</sub>, -CO<sub>2</sub>R<sub>25</sub> (in which R<sub>25</sub> = -SAC, or -SCAC),

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-C(=O)NHR<sub>26</sub> (in which R<sub>26</sub> = -SAC, or -SCAC), and -C(=O)NR<sub>27</sub>R<sub>28</sub> (in which R<sub>27</sub>, R<sub>28</sub> = -SAC, or -SCAC) and can be mono- or poly-substituted at its maximum regardless of the order and the kinds.

2. The compound of formula (I) according to claim 1, in which

- a) R and R' represent hydrogen,
- b) R<sub>1</sub> represents -CH<sub>2</sub>COOH,
- c) R<sub>2</sub> represents (CH<sub>2</sub>)<sub>n</sub>(O)<sub>m</sub>Ar' [in which n=1, 2; m=0, 1; Ar'=substituted phenyl or imidazole], methyl or hydrogen,
- d) R<sub>3</sub> represents -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>COOH, -(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>C(O)NH<sub>2</sub> or -(CH<sub>2</sub>)<sub>2</sub>C(O)NH<sub>2</sub>,
- e) R<sub>4</sub> represents -C(=O)(O)<sub>n</sub>R<sub>29</sub> [in which n=0,1; R<sub>29</sub>=-Ar, or -SAC-Ar], -SO<sub>2</sub>R<sub>30</sub> [in which R<sub>30</sub> = -Ar, or -SAC-Ar], or -C(=O)NHR<sub>31</sub>, [in which R<sub>31</sub> = -Ar, or -SAC-Ar],
- f) X represents -C(=O)CHN<sub>2</sub>, -C(=O)CH<sub>2</sub>Br, -C(=O)CH<sub>2</sub>Cl, -C(=O)CH<sub>2</sub>OAr" [Ar" = phenyl] or -C(=O)CH<sub>2</sub>OC(=O)Ar''' [in which Ar'''=2,6-dichlorophenyl or 2,6-dimethylphenyl].

3. The derivative according to Claim 1, wherein the compound is selected from the group consisting of

- (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;
- (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid;
- (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 1-(N-methyl-N-methoxy)-amide;
- (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-penoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-penoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-penoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-penoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-penoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-sulfonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(2S)-2-acetyl-amino-succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (diastomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-imidazolyl-methyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-

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isoxazole-5-carboxylamino}-4-keto-5-phenoxy-pentanoic acid; and  
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenylcarboxylamino)-propyl]-5-phenyl-  
methyl-4,5-dihydro-isoxazole-5-carboxylamino}-4-keto-5-(1-piperidinyl)-pentan  
oic acid.

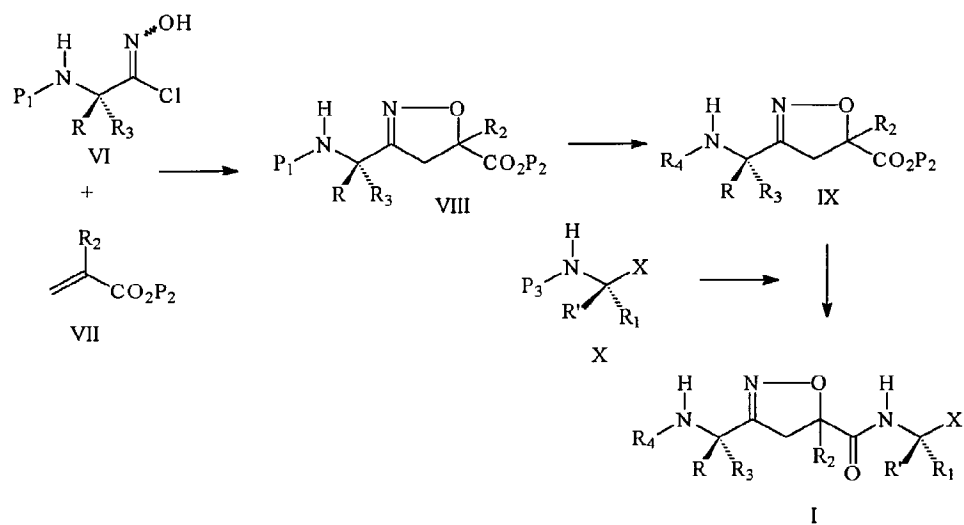
4. A pharmaceutical composition for inhibiting caspases activity which comprises as the active ingredient a therapeutically effective amount of a derivative of formula (1) as claimed in any of Claim 1 to 3 and pharmaceutically acceptable carrier.

5. The composition according to Claim 4, in the form for administration orally, percutaneously, or by parenteral injection.

6. A method of treating patients suffering from the diseases caused by caspases activation, said method comprising the local or systemic administration of a pharmaceutically effective amount of the compound of formula (I) according to any of Claim 1 to 3 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutical carrier.

7. A process for preparing a derivative of the formula (I), which is characterized in that hydroxamoyl chloride (VI) is reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII), and isoxazoline derivative (VIII) is then deprotected and R<sub>4</sub> is introduced therein to give a compound of formula (IX) which is then reacted with a compound of formula (X) and, if necessary, the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and if necessary, the compound of formula (I) having the protecting group P<sub>1</sub> is converted into other compound having substituent R<sub>4</sub>.

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in which the substituents are the same as defined in Claim 1.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 99/00561

<b>CLASSIFICATION OF SUBJECT MATTER</b> IPC <sup>7</sup> : C 07 D 261/04, 413/12, A 61 K 31/42 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC <sup>7</sup> : C 07 D 261/00, 413/00 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AT, Chem. Abstr. Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Questel: DARC, STN: CA, EPO:WPI		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEE et al. "Synthesis of hexapeptide and tetrapeptide analogs of the immunomodulating peptides", J.Chem. Soc., Perkin Trans.1 1998, 359-366 (Eng)., Columbus, Ohio, USA, Chem. abstract, Vol. 128, No.12, 23 March 1998 (23.03.98), page 599, column 2, the abstract No.141000y.	1-7
A	KUSUHARA et al. "Induction of apoptotic fragmentation by non-steroidal anti-inflammatory drugs in cultured rat gastric mucosal cells", Eur. J. Pharmacol. 1998, 360(2/3), 273-280 (Eng)., Columbus, Ohio, USA, Chem. abstract, Vol.130, No.10, 8 March 1999 (08.03.99), page 48, column 1, the abstract No.119256f.	1-7
A	WO 98/49190 A2 (CORTECH INC.) 5 November 1998 (05.11.98) formula I; claim 112.	1-7
A	WO 98/16505 (WARNER-LAMBERT. CO) 23 April 1998 (23.04.98) claims 1,24.	1-7
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: „A“ document defining the general state of the art which is not considered to be of particular relevance „E“ earlier application or patent but published on or after the international filing date „L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) „O“ document referring to an oral disclosure, use, exhibition or other means „P“ document published prior to the international filing date but later than the priority date claimed „T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention „X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone „Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art „&“ document member of the same patent family		
Date of the actual completion of the international search 14 March 2000 (14.03.2000)		Date of mailing of the international search report 11 August 2000 (11.08.2000)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535		Authorized officer Hammer Telephone No. 1/53424/374

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/KR 99/00561

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/46248 A1 (VERTEX PHARMACEUTICALS INCORPORATED) 16 September 1999 (16.09.99) abstract; claims 1,15,20.  -----	1-7

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/KR 99/00561**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although the claim 6 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

PCT/KR 99/00561

Patent document cited in search report				Publication date	Patent family member(s)			Publication date
WO	A1	9816505		23-04-1998	AU	A1	47538/97	11-05-1998
					EP	A1	946502	06-10-1999
					NO	A0	991674	09-04-1999
					NO	A	991674	12-04-1999
					PL	A1	332640	27-09-1999
WO	A2	9849190		05-11-1998	AU	A1	39651/99	08-11-1999
WO	C2	9849190		15-04-1999	EP	A2	979242	16-02-2000
WO	A3	9849190		18-02-1999	US	A	6004933	21-12-1999
					WO	A1	9954317	28-10-1999
					AU	A1	71556/98	24-11-1998
WO	A1	9946248		16-09-1999	AU	A1	29018/99	27-09-1999